THE STABILIZATION OF SYRUP OF FERROUS IODIDE, U. S. P. X

By

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I. INTRODUCTION

Shortly after the discovery of iodine by Courtois in 1811 (1), this element was introduced into medicine by Coindet (2), who satisfied himself that iodine was the active constituent of ashes of sponges, which had long been used empirically in the treatment of goitre and scrofula. Iron has been used in medicine since ancient times (3). Ferrous iodide, a combination of these two elements, was discovered by Courtois (1) who reported its preparation in 1811, and it was introduced into medicine by Dr. Pierquin (4) in 1824, who used the chemical as prepared by Caillot (5), a French pharmacist. Although the compound, administered in the form of pills, wine, tincture, salve, and pastilles achieved excellent therapeutic results, its chemical instability as evidenced by the liberation of free iodine presented a problem to pharmacists which has existed since the introduction of ferrous iodide into medicine.

At the present time, "Syrup of Ferrous Iodide" is official in the United States Pharmacopoeia as well as in most of the pharmacopoeias of the world and enjoys wide popularity as a therapeutic agent.

The purpose of the present investigation was to clarify the mass of information previously published,

to evaluate the methods of preservation previously suggested, and to develop if possible, a more satisfactory preservative than any yet known.

II. HISTORICAL REVIEW

1. Period from 1824-1840.

Following his introduction of ferrous iodide into medicine in 1824, Dr. Pierquin (6) in 1831 recommended the use of ferrous iodide in amenorrhea, scrofula, etc. and published the following formulas as suitable modes of administration:

Chocolate

Ferrous iodide	115 grains
Vanilla chocolate	1 pound.

Water

Ferrous iodide	4 drachms
Water	2 pounds

Pastilles

Ferrous iodide	1 drachm
Saffron powder	4 drachms
Sugar	8 ounces
Tragacanth	q.s.

Salve

Ferrous iodide	2 drachms
Lard	1 ounce

Tincture

Ferrous iodide	2 drachms
Alcohol Water a.a.	2 ounces

Wine

Ferrous iodide	4 drachms
Bordeaux wine	1 pound

Bath

Ferrous iodide	2 ounces
Water	q.s.

Baup and Caillott's (7) formula as prepared by Durand (8) was first introduced into medical practice in Philadelphia by Dr. Samuel Jackson and was known as "Dr. Jacksons Solution of Iodide of Iron". This formula follows:

"Iodine----------10 drachms
Iron filings---------- 5 drachms
Water----------12½ ounces

Put the iodine into a porcelain capsule with one-half the quantity of water above directed, add the iron filings by portions, stirring the mixture with a glass rod ---------. When the whole of the iron has been added, the capsule is put on a sand bath and heated slowly; continuing to stir the liquid."

Dr. A. T. Thompson (9), of the University of London recommended a method in which one part of iron wire was rubbed with three or four parts of iodine, fifteen parts of water gradually added and the entire portion introduced into a flask with an additional portion of iron and distilled water. The solution was boiled until it acquired a pale greenish color and was then filtered. The finished product was said to contain "hydriodate of

protoxide of iron" and to be suitable for medicinal purposes provided the iodine content was previously ascertained. It is thought that this formula and method of procedure was the basis for the original British Pharmacopoeial monograph.

Although the solution of the solid substance, ferrous iodide, proved to be an undoubted success therapeutically, the solution as well as the pure salt was so unstable as to render its dispensing a serious problem. In order to produce a solution that would not deteriorate so rapidly, Frederking (10) published a formula containing sugar and having an iodine strength of 25 %. He stated that one of his colleagues, Hengel by name, had observed that "this syrup becomes brown, and after a time again becomes bright, yet no separation of iron oxide was observed".

The French Pharmacopoeia of 1837 contained ferrous iodide preparations and during this period, other publications appeared concerning the preparation of iodide of iron (11), (12), (13), (14).

2. Period from 1840-1860.

"Solution of Ferrous Iodide" containing five fluid ounces of honey in twenty fluid ounces of finished preparation became official in the 1840 edition of the

United States Pharmacopoeia, the honey being added as a preservative.

Procter (15) investigated the action of lactose, manna, honey, and "uncrystallizable sugar" as preserving agents; Dupasquier (16) used "Syrup of Gum" as a preservative and Beral (17) used simple syrup for the same purpose.

Tozier (18) and Crew (19) gave directions for the quick preparation of the solution and Battley (20) described the preparation of a syrup containing both the iodide and the chloride of iron.

Creuse (21) prescribed the following formula for "Tasteless Iron Iodide" :

Iodine	126.3 grains
Iron filings	q.s.
Iodine	63.0 grains
Citric acid	201.0 grains
Potassium hydroxide	q.s.

Combine the first portion of the iodine with the iron in the usual manner and filter. Dissolve the citric acid in water and add the second portion of the iodine after exactly neutralizing the citric acid solution with the potassium hydroxide. Add the second solution to the first and when the green apple odor has become well developed, evaporate the solution to dryness with gentle stirring. A mass of acicular crystals is obtained.

During this period, there appeared in the Dispensatory (22), a formula for "Syrup of Iodide of Iron" which

was taken from the Edinburgh Pharmacopoeia and contained sufficient sucrose for the preparation to be classed as a true syrup.

Squire (23) recommended the addition of a coil of wire to the preparation but a patient wished to know "Whether the iron screw is to be swallowed whole ?".

Mialhe (24) advised that the solution be evaporated over iron wire until a drop solidified upon removal and then the whole poured into a flask and tightly stoppered.

Wittstein (25) reported that ferrous iodide crystallizes with four molecules of water, and that its solutions may be boiled without decomposition up to a certain point provided iron is present during the boiling, although prolonged heating accelerates the decomposition.

Jonas (26) thought that the addition of a little hydrochloric acid and the use of alcohol as the reaction solvent would give a pure preparation upon evaporation of the alcohol.

In the 1850 edition of the United States Pharmacopoeia, "Solution of Ferrous Iodide" remained official but the honey in the previous formula was replaced by twelve ounces of sugar.

Maisch (27) proposed a theory of the decomposition of the preparation. He thought that not only light but also the action of oxygen decomposed the ferrous iodide. He stated that hydrated oxides of iron were liberated as well as free iodine but that if an altered solution be placed in air tight bottles and exposed to the action of sunlight, the original color and transparency were regained. He concluded that after this treatment, the preparation contained "iodate of sesquioxide of iron".

Chapman (28) discussed the formula and suggested several minor changes but his chief suggestion was that a smaller quantity of iron should be used.

Fougera (29) likewise discussed the preparation at length, and Pile (30) advised filtering the solution of the iodide into boiling syrup.

It was during this period that the use of "Pills of Ferrous Iodide" first became popular. Dr. Christensen of Edinburgh published a formula for such a preparation in 1845 (31), and Wright (32) improved upon it in 1855.

3. Period from 1860-1870.

The 1860 edition of the United States Pharmacopoeia increased the amount of sucrose in the preparation and changed the title to "Syrupus Ferri Iodidi". The

directions called for the addition of two troy ounces of iodine to 300 grains of iron wire placed in water as the reaction medium and final filtration of the solution into syrup heated to boiling. "Pills of Ferrous Iodide" were also official in this revision.

Veza (33) prepared what he called a "Glycerolatum" by triturating 35 parts of iodine with 70 parts of iron and 400 parts of glycerin. From this, he prepared the syrup as required, by adding 4 parts of the glycerolatum to 200 parts of "Syrup of Gum" and 30 parts of orange flower water.

Fougera (34) stated that syrup of ferrous iodide kept at moderate temperatures for a number of hours becomes almost colorless, contains much glucose, is unaltered by air, and behaves toward reagents like an iodide.

In 1864, it was suggested (35) that honey be used in the formula with the addition of citric or tartaric acids and that the preparation be known as "Citromel" or "Tartromel"; fifteen and a half grams of the latter acid was recommended for 426 grams of the preparation. It was stated that this type of preparation keeps well.

Holloway (36) recommended that the preparation be exposed to the sun for a few hours daily, and Tilden (37)

advised the addition of a thin layer of oil to be superimposed on the liquid.

Hughes (38) undertook a series of experiments on the decomposition of this preparation and concluded that when the pharmaceutical is made more concentrated than usual, it undergoes no gradual decomposition provided that it is not corked but covered instead with vegetable parchment.

E.R. Squibb (39) repeated a previous suggestion of F.F. Mayer (40) that sodium hyposulfite be added in order to form hydriodic acid and sodium tetrathionate in a partially decomposed preparation. He also thought that this addition would prevent further decomposition.

Jeannel (41) stated that tartaric acid was the most efficacious substance known for the prevention of the decomposition.

E.R. Squibb (42), as chairman of the U.S.P. revision committee made the following recommendations for the modification of the official process: (a) iron is in too great an excess and should be reduced in quantity, (b) a thin flask as specified is unnecessary, (c) the flask may be cooled to moderate the reaction if necessary, (d) iodine should be added to the iron in small portions, (e) no

heat should be used as it favors the conversion of the sucrose into glucose, and (f) the point of the funnel used in the filtration should descend into the liquid and a wetted double filter should be used.

4. Period from 1870-1880.

Despite the apparent dissatisfaction with the existing formula, no change was made in the 1870 revision of the United States Pharmacopoeia.

Beardsworth (43) stated that a combination of bright light and citric acid would preserve this preparation.

Hunstock (44) worked out a cold percolation process for the manufacture of the solution but it apparently offered no advantages over the existing methods.

Remington (45) offered a formula in which he prepared and added a solution of potassium citrate to the usual solution of ferrous iodide but in this case containing an excess of iodine. The citrate solution was added in just sufficient quantity to cause the solution to become green in color.

Klie (46) amplified and improved the process of Hunstock, while Tizier (47) stated that technique was an important factor in preparing stable preparations and that the faster the manipulation was attended, the better

would be the product.

Wayne (48) observed that grape sugar was sometimes deposited in old samples of syrups containing ferrous iodide and believed this to be due to the presence of hydriodic acid.

Pile (49) contradicted prevalent opinions with the statement that citric acid exerts no preservative effect and that the best means of preservation is the use of sealed, well filled containers, while Judge (50) advised the use of hypophosphorous acid to restore a partially decomposed preparation, it being superior to sodium hyposulfite because in the latter case, half of the sulfur precipitates thus giving the preparation an unpleasant appearance.

Hammer (51) observed that when a solution of ferrous iodide containing some sucrose is brought to the boiling point, a stable preparation results. He attributed the increased stability to glucose formed in the solution by hydrolysis of part of the sucrose.

Rother (52) recommended the addition of the sugar directly to the boiling solution of iodide of iron and the addition of sodium hyposulfite to the finished preparation as a preservative. He expressed the opinion

that the carbon present in the iron wire was objectionable.

Pavesi (53) however, with the broad statement that no known process furnished satisfactory results, submitted a new modification which he claimed to produce an excellent preparation. He prepared first the protochloride of iron from one part of pure iodine and then added iron filings with trituration until the mixture assumed a green color. At this point, he added three parts of egg albumen and five parts of mannite, heated the solution nearly to boiling, filtered, and evaporated to dryness, using the crystals so obtained to prepare the syrup as needed.

Gregory (54) suggested the use of glycerin as a substitute for the simple syrup in this preparation.

5. Period from 1880-1890.

The U.S.P. revision of 1880 described the preparation as "Syrupus Ferri Iodidi", a syrupy liquid containing 10 % of ferrous iodide. It directed that the syrup be made from 25 parts of iron and 82 parts of iodine and the liquid filtered into 600 parts of sugar. The National Formulary of 1880 contained "Solution of Ferrous Iodide", a preparation containing no sucrose but with hypophosphorous acid present as a preservative. It was,

however, dropped from the succeeding revisions.

Groves (55) during his investigations of various means of preservation , discovered that if traces of phosphoric acid are added to the preparation during the reaction, "the peroxide of iron is seized and thus the liberation of free iodine is prevented rendering the syrup stable over a period of some years". He further stated that if the syrup is already discolored, the addition of this acid is of no avail but that if potassium hydroxide is added and then a slight excess of phosphoric acid, the remedy is of advantage.

Runyan (56) gave a series of practical notes on the preparation and offered a new formula which differed only slightly from those already submitted.

Carles (57) reviewed the methods of preservation already offered and decided that what was needed was a substance "like ferrous iodide", insoluble however, and possessing a greater affinity for oxygen than the iodide itself. He finally picked hydrated sulfide of iron as the necessary substance since his experiments showed that it not only preserved the syrup for an indefinite time but was able to restore a discolored syrup to its normal color. He prepared this substance by precipitating a

solution of iron with ammonium sulfide. The precipitate was washed by decantation, collected on a filter and preserved in a bottle in a moist condition. He advised the use of two grams of iron sulfide for 100 c.c. of the finished syrup. He also stated that one gram of citric acid for every 1300 grams of syrup is an excellent preservative.

Schacht (58) was led to believe from his results that glycerin possessed the power to reduce ferric chloride to ferrous chloride. Consequently, he tried glycerin as a preservative but found that it was of no value.

Dr. Francesco (59) suggested the following formula and method of procedure:

Iodine----------	8.0 parts
Iron----------	2.5 parts
Glycerin----------	90.0 parts

Heat the iodine with the glycerin until dissolved and add the iron in small portions maintaining the temperature at 80° C. by means of a water bath. After a dark green color appears, allow the iron to settle, cool and decant.

The author added that the preparation if made by the above formula keeps well.

Izard (60) suggested the addition of a few drops of alcohol as soon as the iron has combined with the iodine. He believed that this produces an aldehyde which prevents

the oxidation of the ferrous salt.

In 1885, an innovation (61) was brought forth in the form of "Tasteless Syrup of Iodide of Iron" which was prepared by adding potassium citrate to a solution of ferrous iodide and then adding iodine until the solution became green. This preparation was said to contain ferric iron.

A.E. Robinson (62) as a result of extensive experimentation, offered the following formula :

Iodine----------	1,804 grains
Iron wire----------	2 ounces
Distilled water----------	6 fluid ounces
Hypophosphorous acid (20 %)-----	3 fluid drachms

The preparation was made in the usual manner and diluted to 8 fluid ounces with water. For use it was combined with simple syrup in the ratio of 1 to 7.

Plevani (63) stated that ferrous iodide dissolved in glycerin undergoes no change and offered a formula based upon this idea.

Miller (64) advised the use of a bright sandpapered iron wire dipped into the liquid during the filtration, and a second wire suspended from the cork into the finished preparation which should be exposed to daylight.

Schmidt (65) reported that a discolored syrup might

be restored to its original condition by boiling it with a small quantity of iron. At the same time, Hebinger (66) proposed a slightly modified formula and Eliel (67) made a suggestion as to technique.

England (68) believed that if glucose would assist in the preservation of "Vallet's Mass" , it would prove to be efficient in the case of ferrous iodide. His results show it to be of some value for this purpose but are not conclusive. England explained the decomposition according to the following equation:

$$2\ FeI_2 + O + H_2O = Fe_2I_2O_2 + 2\ HI$$

wherein a preliminary oxidation to a ferric compound occurs, with subsequent precipitation of ferric hydroxide and the liberation of iodine.

Nicot (69) and Arthur (70) suggested formulas using glycerin as the preservative.

Zelinka (71) stated that if pure distilled water was added in the process of manufacture rather than ordinary tap water, a perfectly stable preparation would result.

Devine (72) performed a series of experiments designed to show the action of hypophosphorous acid on ferrous solutions in the absence of sugar. He prepared

samples of the National Formulary "Solution of Ferrous Iodide" and placed them in filled 1 ounce vials with varying amounts of hypophosphorous acid. These were kept at varying temperatures for 6 months and observations made. Samples prepared in the above fashion and kept at 70 degrees Centigrade were found to be well preserved with 5 to 9 minims of acid per fluid ounce of solution but smaller amounts of acid led to yellow tinged products. Similar results were obtained with samples kept at a temperature of 60 degrees Centigrade. Another series of samples prepared one and one-half times the strength of the National Formulary solution with respect to ferrous iodide and stored under conditions similar to the above showed marked superiority of preservation, 3 minims of the acid per fluid ounce being sufficient to insure a good sample. Half strength samples were next prepared but preservation was found to be much more difficult than in the preceding instances, note being made of a yellow-red deposit in certain cases. Potassium hypophosphite was also tried as a preservative for ferrous solutions but it was found to be utterly worthless, even appearing to accelerate the change.

6. Period from 1890-1900.

Arthur (72) confirmed his previous results as regards the use of glycerin as a preservative, while Good (73)

announced that if the syrup was made with the N.F. Solution there was no tendency toward decomposition.

Warren (74) advocated the use of hypophosphorous acid as a preservative.

Beck (75) stated that the official syrup will not decompose if kept in an atmosphere of carbon dioxide.

Siboni (76) used glucose as a preservative and obtained good results as to the stability of the preparation.

Micas (77) suggested the use of citric acid as a preservative and added that the syrup should be kept in well filled bottles in daylight in a cool place.

Scheerer (78) stated that if pure rock candy syrup is used in the preparation of ferrous iodide syrups and that if cotton covered with glass wool is used as the filtering medium, then the preparation remains unchanged.

Martin (79) offered a twenty minute method for the preparation of this syrup by the use of reduced iron in the formula in place of pure iron. He suggested preservation by means of citric acid.

Martenson (80) and Hanzlik (81) stated that if the

syrup be made with sugar containing ultramarine, it will gradually assume a reddish color. They stated also that if rock candy syrup be used, no trouble would be experienced.

Glycerin was again advocated (82) but with little more experimental evidence than the majority of the previous workers had advanced.

C.T. Roberts (83) called attention to some errors in technique which commonly occur in the manufacture of this preparation.

Rousillon (84) again suggested glycerin as the most satisfactory preservative.

Walker (85) after a series of experiments, concluded that although glucose is a valuable preservative, hypophosphorous acid is even better. He also showed that a mixture of the two is unsatisfactory. Results showed further, that samples preserved in half filled bottles decompose faster than those stored in completely filled bottles.

Citric acid was said by Schobert (86) to be the best preservative if used in the proportion of one part in a thousand parts of finished preparation.

In the seventh revision of the U.S. Pharmacopoeia

which appeared at about this time, we find the iodine increased to 83 parts over the previous 82 parts and in accordance with the suggestions of Squibb (42), the directions called for the point of the funnel to be placed in the sucrose during the filtration. However, despite the experimental evidence in favor of daylight as a preserving agent, directions as to this factor were omitted. This revision marked the introduction of a method of testing the syrup.

Worthrup (87) advised the use of citric acid, (one grain per fluid ounce of the syrup) as a preservative.

Lyon (88) offered evidence that glucose is a satisfactory preservative and stated as a result of his experiments that a sample prepared with 8 % glucose is perfectly preserved. He showed that less glucose than the above amount turns the preparation brown while a greater quantity causes precipitation. These experiments were carried out in part using purified glucose.

Bradley (89) advised that a combination of syrupy glucose and hypophosphorous acid was the most efficient means of preservation.

Levy (90) advocated the use of hypophosphorous acid alone.

Worthrup (91) again published his belief in citric acid as the best preservative and it is noted (92) that the British Pharmacopoeia used hypophosphorous acid for this purpose.

Goodwyn (93) also added that he believed the permanence of a good sample of this preparation which had fallen into his hands was due to the use of some hypophosphorous acid in the process of its manufacture.

In 1894 (94), an article appeared in a foreign journal which suggested the use of citric acid solution previously neutralized with potassium hydroxide.

Barksdale (95) stated that if sugar is added to the solution of ferrous iodide and the whole then filtered into a portion of syrup, the keeping qualities of the syrup are improved.

Dr. Dohme (96) using hypophosphorous acid as the preservative, considered it the most satisfactory and a committee from the American Pharmaceutical Association appointed to consider his findings, reported (97) that this preservative was undoubtedly very satisfactory since it yielded a very stable preparation.

Macy (98) believed that there is no decomposition evidenced by the syrup if it is made according to the

U.S. Pharmacopoeial formula but added that it is necessary to keep the preparation in full sunlight. He also submitted a formula wherein he had replaced 25 % of the syrup by glucose and believed this to furnish a very stable preparation.

Haussmann (99) in remarking on the suggestions and formula suggested by Dohme (96), proposed a formula in which the sugar was reduced from 850 to 600 grams per liter of finished product and dilute hypophosphorous acid was substituted for the concentrated form.

7. Period from 1900-1910

The United States Pharmacopoeial monograph as it appeared in the eighth revision (1900) on this preparation follows:

"SYRUPUS FERRI IODIDI

Syrup of Ferrous Iodide

A syrupy liquid containing about 5 percent., by weight, of Ferrous Iodide (FeI_2 = 307.30), or about 6.74 Gm. in 100 Cc.

Iron, in the form of fine, bright wire, and cut into small pieces, twelve and one-half grammes	12.5 Gm.
Iodine, forty-one and one-half grammes	41.5 Gm.
Diluted Hypophosphorous Acid, twenty Cc.	20.0 Cc.
Sugar, six hundred grammes	600.0 Gm.
Distilled Water, a sufficient quantity,	
To make one thousand grammes	1000.0 Gm.

Introduce the Iron into a flask of thin glass, having a capacity of about five hundred cubic centimeters, add to it one hundred and fifty cubic centimeters of Distilled Water, and afterwards the Iodine. Shake the mixture occasionally, checking the reaction, if necessary, by the affusion of cold water, and , when the solution has acquired a greenish color, and has lost the odor of Iodine, heat it to boiling and add at once fifty grammes of the Sugar; when this has dissolved, filter the solution into the remainder of the Sugar contained in a porcelain dish. Rinse the flask and Iron Wire with one hundred and twenty-five cubic centimeters of Distilled Water and pass the washings through the filter into the Sugar. Stir the mixture with a porcelain or wooden spatula, heating the liquid on a water-bath until complete solution is effected, and, having passed the syrup through a clean muslin strainer into a tared bottle, add the Diluted Hypophosphorous Acid, and sufficient Distilled Water to make the product weigh one thousand grammes.

A transparent, pale green liquid, having a sweet, strongly ferruginous taste and a neutral reaction.

Specific gravity : about 1.349 at 25° C.(77° F.).

On adding a few drops of potassium ferricyanide T.S. to a small portion of the diluted Syrup a blue precipitate will be produced.

If mixed with a little starch T.S., and afterwards with a few drops of chlorine water, the syrup will acquire a deep blue color. This color should not be produced in the Syrup by starch T.S. alone (absence of free iodine)

If 10 Gm. of Syrup of Ferrous Iodide be diluted with distilled water to measure 100 Cc., and 15.4 (15.36) Cc. of the solution be mixed with 15 Cc. of water, 6 Cc. of tenth-normal silver nitrate V.S., and 2 Cc. each of diluted nitric acid and ferric ammonium sulphate T.S., then, after thoroughly shaking the mixture, not more than 1 Cc. of tenth-normal potassium sulphocyanate V.S. should be required to produce a permanent reddish-brown tint (each Cc. of tenth-normal silver nitrate V.S. consumed corresponding to 1 percent. of Ferrous Iodide) .

Average dose.- 1 Cc. (15 minims). "

Lyons (100) stated that samples of Syrup of Ferrous Iodide prepared 6 years previously with 10 % of glucose instead of syrup had kept perfectly.

Madsen (101) stated that colorless glass containers are as good as, if not better, than any other kind for ferrous solutions. His experiments included green glass, ruby red glass and orange glass.

Meridith (102) conducted a series of experiments from which he concluded that glycerin acts as a preservative by preventing oxidation and assimilating any liberated iodine into a non-irritating compound in which form it is taken up by the system after ingestion, as free iodine. He further stated that glucose is the ideal preservative as it not only prevents oxidation but reduces iodine to hydriodic acid after its liberation. He suggested the replacement of the sucrose in the formula by syrupy glucose, adding however, that it must be free from sulfates and chlorides. Specification is also made that the sugar used must be free from ultramarine and that the water used must be free from ammonia.

Debrage (103) discussed the causes of alteration in this preparation and noted that the addition of tartaric acid did not prevent the change from the ferrous to the

ferric state although somewhat retarding it. He verified previous statements that the solution should be kept in the sunlight in filled, well stoppered bottles and believed that a small addition of tartaric acid was advantageous.

Howell (104), in a paper presented to a local association summed up the previous work on this preparation and stated that although few syrups had given so much trouble, little new material had been brought forth. He found that a discolored sample of the preparation could be restored by shaking it with reduced iron in the cold and the syrup thus restored by shaking appeared to keep perfectly. He added that iron and heat will cause the same phenomenon to occur but that in this case, the color is slightly different from that of the original. His recommendation as to preservative was the use of phosphoric acid.

Base (105), thinking that the reported preservative action of glucose was due to impurities contained therein, experimented with dextrose and concluded that this substance and consequently glucose has no preservative action on the syrup. He attributed the successful use of glucose by some workers to the presence of sulfites as impurities.

Schleimer (106) first washed the iron with dilute acid

to remove any alkaline impurities and used rock candy instead of sucrose. He claimed that this gave a permanent preparation.

Caldwell (107) stated that the hypophosphorous acid used in the preparation should, in his opinion, be added after the reaction, but before filtration, so that iron hypophosphite, which he thought to be a better preservative than any other compound, might be formed. He also advised (108) the use of reduced iron in the formula and stated that it allowed the reaction to occur much more readily and completely.

Dunning (109) stated that if syrup of ferrous iodide be allowed to stand in the presence of the excess iron during its manufacture for an hour or more and then heated to boiling and filtered, it never failed to be of a beautiful green color.

8. Period from 1910-1920

Toplis (110) stated that iron wire delays the manufacture of the preparation unnecessarily and recommended reduced iron instead. He also described a method of causing the reaction to go steadily rather than intermittently.

Alpers (111) remarked that no matter how carefully

the ingredients are chosen, the reaction between them will not always proceed alike and added that this is a very peculiar fact in view of the simplicity of the reaction involved.

Thum (112) considered the use of hypophosphorous acid objectionable on the basis that it preserves the preparation too well, thus preventing the liberation of free iodine in the body as the physician desires. He believed that preservatives in all foods and medicines were erroneous for the same reason and followed this amazing statement by another in which he stated that he had prepared a stable syrup simply by doubling the quantity of iron used in the formula.

The United States Pharmacopoeial monograph on syrup of ferrous iodide as contained in the ninth revision (1910) follows:

"SYRUPUS FERRI IODIDI

Syrup of Ferrous Iodide

Syr.Ferr.Iod. - Ferri iodidi syrupus P.I.

A syrupy liquid containing not less than 4.75 per cent. nor more than 5.25 per cent. of FeI_2 (309.68). Preserve it in completely filled, tightly-stoppered bottles.

Iron, in the form of fine, bright wire and cut into small pieces, twelve and five-tenths grammes----------	12.5 Gm.
Iodine, forty one and five-tenths grammes----	41.5 Gm.

Diluted Hypophosphorous Acid, twenty milliliters	20.0 mils
Sugar, five hundred and seventy five grams	575.0 Gm.
Distilled Water, a sufficient quantity,	
To make one thousand grammes	1000 Gm.

Introduce the iron and iodine into a flask of thin glass, having a capacity of about five hundred mils, and add to it one hundred and fifty mils of distilled water. Shake the mixture occasionally, checking the reaction if necessary, by placing the flask in cold water, and, when the solution has acquired a greenish color and has lost the odor of iodine, heat it to boiling and add at once fifty grammes of sugar; when this has dissolved, filter the solution into the remainder of the sugar contained in a porcelain dish. Rinse the flask and iron wire with one hundred and twenty five mils of distilled water and pass the washings through the filter into the sugar. Stir the mixture with a glass rod or a porcelain spatula, heating the liquid on a water bath until complete solution is effected, and, having passed the syrup through a clean muslin strainer into a tared bottle, add the diluted hypophosphorous acid and sufficient distilled water to make the product weigh one thousand grammes.

A transparent, pale yellowish-green, syrupy liquid, having a sweet, strongly ferruginous taste and a slightly acid reaction.

Specific gravity : about 1.35 at 25° C.

Add a few drops of potassium ferricyanide T.S. to 5 mils of Syrup of Ferrous Iodide; a blue precipitate is produced.

Mix 5 mils of Syrup of Ferrous Iodide with a few drops of starch T.S. and add 3 drops of chlorine water; the liquid acquires a deep blue color. No blue color is produced in the syrup by starch T.S. alone (free iodine).

Assay - Dilute about 10 grams of Syrup of Ferrous Iodide, accurately weighed, with 30 mils of distilled water, add 50 mils of tenth-normal silver nitrate V.S., and 5 mils of nitric acid and heat on a water bath until the precipitate of silver iodide is yellow. Cool, add 2 mils of ferric ammonium sulphate T.S., and determine the residual silver nitrate by titration with tenth-normal potassium sulphocyanate V.S. It shows not less than 4.75 per cent. nor more

than 5.25 per cent. of FeI_2.
Each mil of tenth-normal silver nitrate V.S. used corresponds to 0.015484 Gm. of FeI_2. Each gramme of Syrup of Ferrous Iodide corresponds to not less than 3.07 mils nor more than 3.4 mils of tenth-normal silver nitrate V.S.

Average dose - Metric, 1 mil - Apothecaries, 15 minims. "

Alpers (113) as a result of some experimentation concluded that : (a) the presence of a catalyst during the reaction is desirable and a coil of bright iron wire is the most practical, (b) the sucrose should be dissolved in the liquid at the boiling temperature and further heating is non-beneficial, (c) the finished syrup should be kept in small well filled bottles in ordinary daylight, the color of the glass used being immaterial, (d) neither glucose nor invert sugar is desirable as a substitute for cane sugar, (e) the preparation needs no preservative if it is made from the best of ingredients and hypophosphorous acid neither helps nor hinders preservation, (f) after the bottles are opened, citric acid is the best preservative, nevertheless the preparation spoils rapidly after 30 days, and (g) loss of ferrous iodide content is very slight even after color changes have occurred.

O.J. Cloughly (114) advocated the shaking of the iron wire with a solution of potassium hydroxide before

allowing it to react with the other ingredients. He stated that this freed the iron from any and all ingredients which caused the preparation to darken. He advised the use of citric acid as a preservative and stated that hypophosphorous acid forms iron hypophosphite which in turn causes the preparation to turn dark but that citric acid forms iron citrate, thus giving the required green color.

Dr. Noblet (115) discovered that if the syrup be made up with 1 % of alcohol and kept in bright sunlight, it showed no disposition to change.

Bohrisch (116) advocated the use of an iron spatula, which he considered a catalyst for the reaction, to be dipped into the reaction mixture. He stated that such a procedure caused the reaction to go smoothly and easily to completion. At the same time he advised the use of citric acid as a preservative.

9. Period from 1920-1933

The United States Pharmacopoeial monograph on syrup of ferrous iodide as it appeared in the tenth revision (1920) and which is now official follows:

*SYRUPUS FERRI IODIDI

Syrup of Ferrous Iodide

Syr.Ferr.Iod. - Ferri Iodidi Syrupus P.I.

Syrup of ferrous iodide contains not less than 6.5 grams and not more than 7.5 grams of FeI_2 in each 100 cc., representing approximately 5 per cent of FeI_2 by weight.

Iron, in the form of fine, bright wire	20 Gm.
Iodine	60 Gm.
Hypophosphorous Acid	5 cc.
Sucrose	850 Gm.
Distilled water, a sufficient quantity,	
To make	1000 cc.

Place the iron in a flask having a capacity of about 500 cc., add the iodine and 200 cc. of distilled water, and shake the mixture occasionally, checking the reaction if necessary by placing the flask in cold water. When the liquid has acquired a green color and has lost the odor of iodine, heat it to boiling, and dissolve 100 Gm. of sucrose in the hot liquid. Filter the solution at once into a flask graduated to 1000 cc. and containing the remainder of the sucrose, and rinse the flask containing the iron with 240 cc. of hot distilled water, in divided portions, passing the rinsings successively through the filter. Agitate the mixture until the sucrose is dissolved, warming if necessary, cool to 25° C., add the hypophosphorous acid and enough distilled water to make the product measure 1000 cc. Mix well and strain.

Description and physical properties - A transparent, pale yellowish-green, syrupy liquid having a sweet, strongly ferruginous taste and a slightly acid reaction.

Specific gravity : 1.37 at 25° C.

Test for identity - Add a few drops of potassium ferricyanide T.S. to 5 cc. of the Syrup of Ferrous Iodide : a blue precipitate is produced.

Mix 5 cc. of Syrup of Ferrous Iodide with a few drops of starch T.S. and add 3 drops of chlorine T.S.; the liquid acquires a deep blue color.

Test for purity - No blue color is produced in Syrup of Ferrous Iodide by starch T.S. alone (free iodine).

Assay - Place exactly 10 cc. of Syrup of Ferrous Iodide in a flask, dilute it with 30 cc. of distilled water, add 50 cc. of tenth-normal silver nitrate and 5 cc. of nitric acid, and heat on a water bath until the precipitate of silver iodide is yellow. Cool, add 2 cc. of ferric ammonium sulphate T.S., and determine the residual silver nitrate by titration with tenth-normal potassium thiocyanate. Each cc. of tenth-normal silver nitrate corresponds to 0.01548 Gm. of FeI_2.

Preserve in completely filled, tightly-stoppered bottles.

Average dose - Metric, 1 cc. - Apothecaries, 15 minims.

Examinations of commercial samples of syrup of ferrous iodide from time to time have shown serious deterioration (117), (118), (119), (120), (121), (122), (23).

In an attempt to evaluate the preservatives citric, tartaric, and hypophosphorous acids, Beringer (123) prepared a series of samples of the preparation using these substances in the manufacture. He found that a U.S.P. sample although it turned slightly yellow in 2 months, had resumed its original pale green color in 8 months. The sample prepared according to the U.S.P. VIII method evinced a yellow color in 8 months and he attributed this change to caramelization of the sugar, stating that this was due to the presence of the hypophosphorous acid. He failed to note any changes in the samples prepared using citric and tartaric acids as preservatives.

Kaemmerer (124) undertook a study of preservatives and tried citric acid as well as glucose and combinations of both. He concluded that citric acid retarded the change somewhat but actually had no permanent preservative effect. Subsequent trials with 25 % glucose and a mixture of 25 % glucose and 1 % citric acid gave similar results. He found however, that a syrup made by the U.S.P. directions did not change.

Haussmann (125) concluded that the discoloration is due to caramelization of the sugar and only in exceptional cases due to oxidation of the salt. In an examination of fifteen discolored samples, not one reacted for the presence of ferric compounds. He added that moreover, this is not the only iron preparation causing darkening in sugar solutions and cited a syrup of ferrous sulfate which also turned dark but did not react for ferric compounds.

Berg and Becker (126) gave evidence to support Haussmann's view when, in 1929, they conducted a series of experiments designed to show whether or not it was oxidation which caused the darkening in this preparation. They prepared a syrup using boiled distilled water and placed it in two ounce bottles. Half of these were evacuated by a pump and the vacuum broken with nitrogen.

The two sets were stored under various conditions. In three months, darkening occurred in all samples stored at room temperature but not in the samples stored in the refrigerator. In nine months , samples stored in the refrigerator had darkened but the test for free iodine was negative, thus leading the authors to think that this might be a process of caramelization. To test the theory that hypophosphorous acid causes discoloration in sugar solutions, two series of experiments were run, the first series of samples containing hypophosphorous acid and the second series containing citric acid (3 grams per 1000). In four months a definite darkening occurred in the U.S.P. samples but there was no change in those preserved by citric acid. Neither group contained free iodine. The authors cited the pharmacopoeias of Holland, Austria, Switzerland, Belgium and Hungary as evidence that citric acid is popular as a preservative. They concluded that darkening is really caramelization rather than oxidation.

Arny and Steinberg (127) further support this viewpoint with the statement that darkening is due to the hypophosphorous acid mistakenly added as a preservative and that this chemical does not preserve the preparation longer than 2 or 3 months after which time it assumes a permanent brown color. They added that samples without

the acid, although they turn brown in a few days due to the liberation of free iodine, can easily be restored to the original color by exposure to sunlight.

The facts presented above by Arny and Steinberg are difficult to reconcile with those presented in a later article by the same authors. They found (128) that although this preparation shows discoloration in one month when exposed to direct daylight, regardless of the color of the bottles, it is stable in diffused light for one year or more.

Bradford and Langenhan (31) conducted an investigation in which a series of samples was prepared using varying proportions of the ingredients. The appearance of these samples at the time of manufacture was noted and compared with their appearance at the end of five months. They found that a sample made without the use of hypophosphorous acid turned brown at the end of this time and showed traces of free iodine whereas a sample prepared by the U.S.P. method remained pale green in color. Samples prepared by the use of molecular proportions of iron and iodine appeared to keep no better, if as well, as the ordinary preparations. Results along this line were however, inconclusive at best.

Arny, Vener and Jayne (129) conducted a four year

study of the stability of syrup of ferrous iodide. Their results follow: A sample prepared according to the U.S.P. method and kept in filled containers assumed a "ferric yellow color", then turned dark brown at the end of 22 months although analyses showed no free iodine at any time during this period. A similar sample kept in a partially filled container also turned brown at the end of 22 months without showing the presence of free iodine. Neither of these samples were bleached by sunlight. A second sample prepared according to the U.S.P. method but without hypophosphorous acid and kept in filled containers was preserved perfectly at the end of 22 months although free iodine had appeared in the preparation at the end of 2 weeks and had remained until about 20 months storage time. A similar sample, stored in partially filled containers appeared yellow-brown in 20 months but had returned to a green color in 22 months. Iodine was present in this sample until the 22 months period had elapsed. In the case of these samples, it was stated that iodine may be put back into combination by bleaching in sunlight but that it again appears upon placing the preparation in darkness. Another sample prepared using a combination of glycerin and sugar as preservatives but without hypophosphorous acid showed free iodine in 2 weeks. This iodine however, disappeared at the end of 20 months.

Another sample prepared presumably with molecular quantities of iron and iodine showed a yellow-brown coloration in 19 weeks but no further observations were made and consequently the results are inconclusive. A sample made with invert sugar kept perfectly showing no free iodine at any time. Interpreting their results, the authors concluded that: first, the U.S.P. product turns yellow in color and shows traces of a precipitate (a scum, previously noted by Arny and coworkers, had been attributed to dirty bottles); second, the iodide content of all samples was reasonably constant; third, some evidence existed that the scum appearing was ferric hypophosphite; fourth, a syrup prepared without a stabilizer such as hypophosphorous acid, although liberating free iodine, can be returned to normal by the use of direct sunlight; fifth, the U.S.P. syrup showed more decomposition than did the other samples; sixth, omission of hypophosphorous acid or the addition of glycerin is unsatisfactory; seventh, the sample prepared with invert sugar was in good condition at the end of 22 months thus suggesting the possibility that this substance might prove to be a good preservative.

Krantz (130), thinking the decomposition to be due to atmospheric oxidation, determined the amount of sugar inverted from time to time in this preparation and found that in a sample prepared without hypophosphorous acid

the percentage of invert sugar was 10.96 % in 75 days while in a preparation containing hypophosphorous acid, 94.2 % at the end of 10 days and 96.2 % at the end of 20 days was found to be inverted. He concluded therefore, that rapidity of inversion is a function of the pH of the solution. Colorimetric determinations showed the pH of a U.S.P. sample to be pH 2.8 to pH 3.2 while the sample with hypophosphorous acid omitted showed a pH of 5.2. Due to this fact and the subsequent caramelization of sucrose or glucose, Krantz believed it necessary to find some other preservative than sucrose. Samples were prepared with various percentages of glucose and tested for their resistance toward oxidation by hydrogen peroxide (3 % solution) by oxidizing with excess peroxide and titrating the liberated iodine with thiosulfate solution. Results showed conclusively that pure glucose in the form of dextrose has no superiority over sucrose in the matter of preservation. A series of samples were next prepared using various other media and tested for resistance to oxidation as before. A relationship was drawn between the viscosity of the medium and the ease of oxidation by hydrogen peroxide. A solution prepared with mucilage of acacia offered by far the most resistance with glycerin next in order. These results were verified by electrolyzing certain preparations of glycerin and sucrose and the

superiority of glycerin over sucrose was further indicated by the fact that a sample prepared with 40 % glycerin had kept perfectly for a period of 9 years. Krantz calculated the molarity of the solutions with respect to sucrose and glycerin concentrations and concluded that increase in preservative action is probably due not to any chemical properties of these substances but rather to an enveloping action of the molecules. A statement was made to the effect that the resistance of the preparation toward oxidation varies directly as the viscosity of the solution and the number of mols of the protective substance, and inversely as the amount of surface exposed to the air. Mathematically, this may be expressed :

$$R \propto \frac{N\,V}{S}$$

where "R" is the resistance of the preparation to oxidation, "V" is the viscosity of the solution, "N" is the number of mols of protective substance and "S" is the amount of surface exposed to the air.

10. Variations in Pharmacopoeial Monographs.

The following tabulation offers a summary of the various changes that have occurred during the 60 years in which 'Syrup of Ferrous Iodide' has been official. All data except that for the 1860 and 1870 revisions of the U.S.P.,

when the preparation was made up to volume rather than weight, have been recalculated to a basis of 1000 Gm. of finished product.

Table 1.

Variations in Quantity of Reactants and of Ferrous Iodide.

Year	Iron	Iodine	Iron required	Excess iron	Fe I_2	Product
1860	30.2	100.0	21.9	9.3	128.0	1000 cc.
1870	30.2	100.0	21.9	9.3	128.0	1000 cc.
1880	25.0	82.0	18.1	6.9	100.1	1000 Gm.
1890	25.0	83.0	18.1	6.9	100.1	1000 Gm.
1900	12.5	41.5	8.9	3.6	49.5	1000 Gm.
1910	12.5	41.5	9.1	3.4	50.4	1000 Gm.
1920	14.6	43.8	9.6	5.0	53.1	1000 Gm.

As indicated in Table 1. the percentage of ferrous iodide in the syrup was reduced in the 1880 revision from 12.8 % to 10.01 % and since 1900, the ferrous iodide content has been approximately 5 %.

The method of preparation has varied somewhat since 'Syrup of Ferrous Iodide' was first introduced into the U.S.P. in 1860. Following is a brief resume' of the different methods that have been official :

A. Order of mixing- The 1860 and 1870 revisions

directed that the iron, iodine and water be mixed together. The next three editions specified the addition of water to the iron before the iodine was added. The 1910 and 1920 revisions directed that the water be added to the iron and iodine.

B. Size and type of flask- Thin glass flasks were specified to be used for the reaction mixture in each revision except the last. All revisions from 1890 on specify the use of a 500 cc. flask for the reaction mixture.

C. Amount of water used for the reaction- The first two formulas used 3 fluid ounces (about 90 cc.). In 1880, 20 parts of water were used and then until the 1920 revision, 150 cc. of water were directed to be added. The last revision however, called for the use of 200 cc. of water.

D. Filtration- In the 1860 and 1870 revisions, it was directed that the solution or reaction mixture be filtered through a small funnel inserted in the neck of a graduated flask that contained syrup and had previously been heated to boiling. In 1880, the directions were modified to specify that the solution was to be filtered at once into a porcelain capsule containing the sugar.

In 1890, a strong double acting filter was specified, the point of which dipped below the surface of 600 Gm. of sugar contained in a tared dish. The succeeding revisions of 1900 and 1920, added 50 Gm. of sugar to the reaction mixture and directed that it be filtered into the remainder of the sugar. In the last revision (1920) the quantity of sucrose added to the hot reaction mixture has been increased to 100 Gm. and filtration performed into a flask containing the remainder of the sugar.

E. Rinsing the flask- All editions of the Pharmacopoeia since 1880 specified that the flask and the excess iron are to be rinsed with distilled water, except the 1890 revision which used a mixture of 25 cc. of syrup and 25 cc. of water for this purpose. The 1920 revision specified that the washing be done with the water in divided portions.

F. Application of heat- Heat is directed to be applied to the reaction mixture in the revisions of 1880, 1890, 1900, 1910 and 1920.

Bourquelot (131) compared ferrous iodide syrups as found in the pharmacopoeias of Greece, France, Belgium, Italy, Spain, Switzerland, Germany, Russia, Austria, England, Denmark, Hungary and Holland.

11. Summary of Suggested Preservatives.

To summarize, the following means of preservation have been suggested in the literature for preparations containing ferrous iodide: changes in proportion of ingredients, the use of glycerin, the addition of hypophosphorous acid, the replacement of a part of the sucrose by glucose or dextrose, the addition of citric or tartaric acids, the removal of impurities from the iron wire used in the formula, the use of reduced iron rather than iron wire in the manufacture, the use of honey as a protective agent, variations in the sucrose content, the addition of small quantities of alcohol, storage in bottles having the air above the liquid replaced by carbon dioxide, the addition of egg albumen and mannite to the dry salt, the addition of hydrated sulfide of iron to the finished preparation, storage in daylight or sunlight, the addition of sodium thiosulfate to the finished preparation, the use of phosphoric acid, the use of potassium citrate and the substitution of rock candy or rock candy syrup for the sucrose in the formula.

III. THEORETICAL PART

1. Iron Compounds

The Properties of Ferrous Iodide. Ferrous iodide is a crystalline, exceedingly deliquescent, solid salt composed of two atoms of iodine in combination with one atom of iron. It occurs as transparent green tabular crystals or as an opaque mass of iron-gray color and metallic lustre, the latter form being obtained by fusing and cooling the former. It is readily soluble in water, ether and alcohol, dissolving to give pale green solutions, but relatively insoluble in chloroform and benzene (131). It is not volatile (132) and has a specific gravity of 2.873.

Ferrous iodide forms several hydrates with water. Lescoeur (133) listed hydrates with 6, 2 and 1 molecules of water respectively, while Volkmann (134) stated that the m.p. of the compound $FeI_2 \cdot 9\ H_2O$ was from 0° to 2.5° C., that of $FeI_2 \cdot 6\ H_2O$ was about 8° C., and that of $FeI_2 \cdot 4\ H_2O$ lay between 90° and 98° C. The anhydrous salt melts at 177° C. (135).

Ferrous salts in general can be oxidized by nitric acid, chlorine, bromine, potassium dichromate, potassium permanganate and other agents to the ferric state. It appears however, that this is not a means for the

preparation of ferric iodide due to the side reaction liberating free iodine when ferrous iodide is treated with an oxidizing agent.

Since ferrous iodide is the salt of a strong acid and a weak base, hydrolysis occurs in its solutions as shown by Krantz (130) and Phillips (137).

Upon heating ferrous iodide in either solid form or concentrated solution in the presence of air, iodine is vaporized and ferric oxide remains behind (137).

The Preparation of Ferrous Iodide. Theoretically, ferrous iodide may be made by: (a) solution of iron in hydriodic acid, (b) action of iron upon the iodide of any metal below it in the electrochemical series, (c) action of ferrous hydroxide upon hydriodic acid, (d) action of ferrous hydroxide on an iodide, the metallic radical of which must form an hydroxide which is volatile, or more insoluble, or less active than ferrous hydroxide, (e) the displacement of halogen having an atomic number greater than that of iodine from an iron halide by the action of iodine, (f) action of hydriodic acid on an iron salt provided that one of the products be volatile, slightly active, or insoluble, (g) double decomposition between two salts, provided that one of the products is insoluble, (h) direct union between iron and iodine (138).

Considering the above methods of preparation, method 'a' is impractical because of the difficulty of preparing pure hydriodic acid in concentrations sufficient to dissolve iron rapidly enough to avoid decomposition of the acid; method 'b' is not feasible because of the slowness of the reaction; 'c' and 'd' are not desirable because of the instability and difficulties in the manufacture of pure ferrous hydroxide; 'e' is impossible at present since no halogens or iron halides are known in which the halogen has an atomic number greater than that of iodine; 'f' is not used since no product volatile without heat is readily formed; 'g' requires extreme accuracy in the proportions of the reacting salts in order to obtain a pure preparation and the insoluble substance formed must be absolutely insoluble; 'h' offers the most practicable means for the formation of the compound.

When iron and iodine combine directly in aqueous solution, they react with the evolution of 47,650 calories, this value representing the sum of the heat of formation and the heat of solution. A comparative value for ferric hydroxide is 23,850 calories, indicating the superior stability of the reduced over the oxidized state. The comparative instability, however, is emphasized by a comparison with the corresponding value for ferrous chloride, i.e., 100,050 calories (139).

Serrulas (140) passed iodine and steam through a red hot iron tube filled with charcoal. He described the product as shining yellow crystals, while Gay-Lussac and Davy (141) stated that it is a brown mass fusing at red heat and subliming at higher temperatures.

A.T. Thompson (142) treated one part of iron with two parts of iodine suspended in water and after evaporating the water in a flask containing some excess iron, obtained a gray mass, m.p. 177° C., having a sharp, puckering taste.

Carius and Wanklyn (143) placed iron filings in a well covered crucible, heated briskly to red heat and after the introduction of a small quantity of iodine (to drive out the air), additional iodine was introduced and the melted mass heated until no more iodine vapor appeared. The crucible was allowed to cool and the product was described as a red-brown, almost black, leafy mass which upon exposure to air became gray in color and gradually changed to a brown liquid. They noted, during the cooling process, a sudden appearance of iodine vapor which they thought to be due to the decomposition of a higher iodide of iron stable only at red heat.

DeLuca (144) described the substance as a pure white amorphous powder while Erdmann (145) stated that it was a reddish-brown body.

Volkmann (146) obtained green crystals deliquescing rapidly in air, by the evaporation of a solution at 0° C.

Jackson and Derby (147) obtained excellent yields of pure ferrous iodide by passing iodine vapors over red hot iron in the absence of oxygen. Nitrogen was used to carry the iodine vapors and it was found necessary to remove all traces of oxygen by passing the gas over copper oxide at high temperatures.

The United States Pharmacopoeia, tenth revision, directs that ferrous iodide be made by direct combination between iron and iodine in aqueous solution, but many investigators have reported that the reaction does not go uniformly to completion.

Other Iron Compounds Involved. Ferrous and ferric hydroxides are classified chemically as weak bases but ferric salts are more readily hydrolyzed than are ferrous salts since $Fe(OH)_3$ is a less active base than is $Fe(OH)_2$ (148).

Ferrous hydroxide is precipitated from solutions of ferrous compounds by alkali hydroxides as a greenish-white precipitate. It changes first to dirty green (hydrated ferroso-ferric oxide) and then to reddish-brown ferric hydroxide (149). Britton and Thomas (150), stating that

various methods for the determination of the basic strength of hydroxides have given inconsistent results, studied the hydrogen ion concentration where precipitation occurred by measuring the E.M.F. with the hydrogen electrode. They found that ferrous hydroxide precipitates at pH 5.5, the value being independent of the nature of the anion or precipitant and affected only slightly by the concentration.

Ferric hydroxide appears as a brownish-red magma when precipitated from a ferric salt with an alkali hydroxide. On boiling, it becomes more compact, gives up water and becomes a basic hydroxide $Fe_2O(OH)_2$ or $Fe_2O_3 \cdot 2\ H_2O$. Freshly precipitated ferric hydroxide readily dissolves in various organic acids such as citric and tartaric acids or their acid salts (151).

The solubility products of the two iron hydroxides follow (152) :

$$Fe(OH)_2 \longrightarrow (Fe^{++})(OH^-)^2 = 1.6 \times 10^{-14}$$

$$Fe(OH)_3 \longrightarrow (Fe^{+++})(OH^-)^3 = 1.1 \times 10^{-36}$$

although Von Weimarn (153) has shown that the case of ferric hydroxide may show some variation in the actual precipitation point.

Seidell (154) lists the solubility of ferric hydroxide in a 50 % solution of sucrose as 2.3 milligrams per liter.

Although data are not available for higher concentrations, the solubility curve rises with increasing sucrose concentration and it is safe to assume that in Syrup of Ferrous Iodide, the solubility will be at least this great. Transforming the value into terms of molarity:

$$0.0023/106.86 = 0.0000218 \text{ mols/L.}$$

and assuming complete dissocation of ferric hydroxide at this concentration, there are present for each gram ion of ferric ion, three gram ions of hydroxyl, and the solubility product is:

$$K_s = (2.18 \times 10^{-5})(6.54 \times 10^{-5})^3 = 6.10 \times 10^{-18}$$

Goodwin (155), in working on the hydrolysis of ferric chloride, concluded that colloidal ferric hydroxide apparently accelerated the whole process of hydrolysis.

Wagner (156) thought that in the hydrolysis of ferric chloride, ferric hydroxide was present partially as $Fe(OH)Cl_2$ and partially as $Fe(OH)_2Cl$. Quartaroli (157) verified Wagner's results and added that in his opinion, the reactions of Fe^{+++} differed from those shown by $(FeOH)^{++}$ and $(Fe(OH)_2)^{+}$. The degree of hydrolysis of ferric chloride at equilibrium was found to be 94.8 % to 100.0 % at a molar concentration of 0.000109 with respect to ferric

chloride and equilibrium was attained within a short time. It was noted that the presence of hydrochloric acid made no difference in the degree of hydrolysis.

Krause and Buczkowski (158) investigated the structure of the yellow hydroxide obtained by the hydrolysis of solutions of ferric chloride at temperatures of 120° to 160° C. They concluded that the hydroxide may be considered as ferrous acid, $HFeO_2$, in which the hydrogen is replaceable by silver. The isoelectric point was found to be pH 5.2 and the ferrous acid remaining in the strongly acid ferric chloride solution after hydrolysis is positively charged so that the formation of a basic chloride is possible. The structure of the yellow hydroxide was said to be:

$$\begin{bmatrix} H\ FeO_2\ (\gamma) \\ Cl \quad H_2O \end{bmatrix} FeO \cdot Cl^-$$

Hydrolysis of the ferric chloride solution at temperatures above 160° C. was shown by these authors to furnish black-violet α-Fe_2O_3 in addition to the yellow compound.

Malfitano and Michel (159) found that nitric acid, sulfuric acid, arsenic acid, phosphoric acid and oxalic acid tend to diminish the irreversible hydrolysis of ferric chloride.

Wintgen and Biltz (160) prepared a series of ferric hydroxide sols from ferric chloride and ammonia and found the hydrogen ion concentration to be invariably 3.8×10^{-4} corresponding to pH 3.4. Concentration apparently exerted little or no effect upon the values obtained. All measurements were made using glass electrodes.

Warynski (161) working on ferrous sulfate, stated that ferrous salts are very resistant to oxidation even though heat be applied. It was found that solutions of ferrous sulfate showed only 1 % to 1.4 % oxidation in four months at ordinary temperatures.

Languepin (162) investigated the action of low temperatures upon samples of ferrous sulfate which had become discolored due to oxidation. He found that upon exposure to cold, such samples consolidated to a greenish- white mass which thawed upon warming to give apparently pure ferrous sulfate.

Poiteven (163) found that reduction from the ferric to the ferrous state could be effected by alcohol, ether, ammonium acetate, alloxantin, glycerin and tartaric acid.

Moldenhauer and Mischke (164) stated that the high velocity of reduction of ferric salts by hydrogen sulfide

in neutral or weak acid solutions was noticeably reduced by the presence of acid. They found that in the presence of phosphoric acid, the reduction takes place as a trimolecular reaction and that the retarding action of the acid is due not to increases in hydrogen ion concentration, but rather to the formation of unknown complexes between iron and phosphoric acid.

Cornog and Hirschberger (165) determined the influence of the hydrogen ion concentration on the oxidation of ferrous sulfate. They dissolved definite quantities of ferrous sulfate in buffered solutions and aerated for 3 hours. Unoxidized iron was determined by the permanganate method. It was found that the amount of oxidation varied both with the initial concentration of ferrous sulfate and with the hydrogen ion concentration of the solution, little or no iron being oxidized in solutions having a value less than pH 5. In solutions buffered to pH 5, the amount of iron oxidized increased with increasing iron concentration. Solutions buffered to pH 10 however, showed the converse to be true. A mathematical expression showing the relationship between the amount of iron oxidized and the time of aeration was developed:

$$\ln T = 0.032 x - 0.01$$

where "x" is the per cent of oxidized iron after "T" hours aeration.

Belloni (166) has stated that when ferric hydroxide is dissolved in an equimolecular mixture of citric acid, a ferricitrate that contains a tri-ferri-dicitrato cation is formed analagous to:

$$\left[Fe_3 \begin{matrix} (CH_3COO)_6 \\ (OH)_2 \end{matrix} \right] (CH_3COO) \cdot H_2O$$

Paira (167) stated that tartaric acid forms compounds with complex anions:

$$\left[Fe\ (C_4H_2O_6) \right]\ H$$

and contains as shown, tartrato ferric acid. Alkali salts of this acid result upon the addition of a base.

Friede showed (168) that iron compounds form salts with certain decomposition products of sugars. He prepared ammonium ferric mucate and ammonium ferric malate by treating the acid in ammonia solution with freshly precipitated ferric hydroxide.

Other complexes of this type have been mentioned in the literature (169), (170), notably those of iron with lactic, glycuronic, oxalic, malic, citric and tartaric acids.

Spencer and Pickering (171) stated that solutions of ferric hydroxide in varying proportions of citric, tartaric, and malic acids show that salts of the type $R''_3\ Fe_2$ are formed which possess great color intensity. They contain the iron in the negative ion and resemble the corresponding cupri- compounds in behavior. Alternative formulas are given:

(1)

$$: (CO_2)_2 : \begin{matrix} C\text{-}(OH)_2 \\ Fe\text{-}O \end{matrix}$$
$$: (CO_2)_2 : \begin{matrix} Fe\text{-}O \\ C\text{-}(OH)_2 \end{matrix}$$

(2)

$$\begin{matrix} C\text{-}(OH)_2 \\ Fe : O \end{matrix}$$
$$: (CO_2)_2 :$$
$$\begin{matrix} Fe : O \\ C\text{-}(OH)_2 \end{matrix}$$

They stated that large proportions of alkali can be added to solutions of the ferric compound without causing precipitation or alkalinity to phenolphthalein, but that when ferric hydroxide is added, insoluble basic salts are gradually precipitated, the decomposition of the ferri-tartrate being the most complete.

Roszkowski (172) investigated the peptizing action of 111 organic compounds on ferric hydroxide and found that of this number, 25 prevented the precipitation. These compounds were polyacid alcohols, carbohydrates, hydroxy monobasic and polybasic acids. It was found that the monobasic and polybasic organic acids prevented the precipitation of ferric hydroxide only in acid or neutral solution. Most of the peptizing compounds were members of

the aliphatic series and contained an hydroxyl group, the replacement of which caused a loss of peptizing power. Twenty-two compounds were found to prevent precipitation from ferric chloride solutions but only 9 were satisfactory in preventing precipitation from ferrous sulfate solutions. Monohydric alcohols were invariably without influence but beginning with glycol, the peptizing effect is proportional to the number of hydroxyl groups.

2. Hypophosphorous Acid and the Hypophosphites.

Hypophosphorous Acid. Hypophosphorous acid although containing three atoms of hydrogen is monobasic and the phosphorous is in the pentavalent state. It forms salts with the metals, ferric hypophosphite being prepared by dissolving ferric hydroxide in the acid and evaporating until crystallization takes place. Hypophosphorous acid is a powerful reducing agent, strongly acid in reaction, and decomposes on heating to phosphine and phosphoric acid (173). Putnam (174) has stated that the acid is relatively non-toxic to animals.

A. Duncan Mitchell (175) has expressed the ionization of hypophosphorous acid in the presence of extraneous hydrogen ions as:

$$\frac{(H^+)(H_2PO_2^-)}{(H_3PO_2)} = 0.1015 - \left[1/35 \log_{10} \frac{\alpha}{(H)}\right]$$

Although the generally accepted theory for the reaction between iodine and hypophosphorous acid is represented (176) :

$$H_3PO_2 + 2\ I_2 + 2\ H_2O \rightarrow H_3PO_4 + 4\ HI\ ,$$

Boyer and Bauzil (177) have shown that this reaction occurs only in solutions which have first been acid and then rendered alkaline. They illustrate the reaction as occurring in two stages, the first in acid media:

$$H_3PO_2 + I_2 + H_2O \rightarrow H_3PO_3 + 2\ HI\ ,$$

and the second in alkaline media:

$$H_3PO_3 + I_2 + H_2O \rightarrow H_3PO_4 + 2\ HI\ ,$$

Weinland and Hieber (178) prepared some complexes of trivalent iron with hypophosphorous acid in which the complex occurred in some cases as the cation and in others as the anion. This phenomenon, previously known only for formic and salicylic acids, is ascribed by the authors to the structural similarity between the two acids, formic and hypophosphorous :

1. $H\text{-}\overset{\overset{O}{\|}}{C}\text{-}H$ 2. $H_2{=}\overset{\overset{O}{//}}{P}\text{-}H$

The Hypophosphites. The hypophosphites are in general, soluble in water and gradually oxidized in solution by atmospheric oxygen to phosphates. Sucrose, however, retards this oxidation. Ferric hypophosphite is practically insoluble in water but is soluble in solutions of alkali citrates (179).

3. Hydriodic Acid.

Hydriodic acid or hydrogen iodide was recognized by Clement and Desormes (180) in 1813. It exists as a colorless gas or associated with one, two or three molecules of water as a colorless liquid, very soluble in alcohol and water. The heat of formation from its elements is -6,400 calories and the heat of solution is 19,600 calories (181), thus offering an indication of its instability.

Lemoine (182) in 1877 reported that an aqueous solution of hydrogen iodide is not changed by the influence of light if air is absent, but that in the presence of oxygen or air, slow decomposition takes place in the light as well as in the dark.

J. Pinnow (183), in 1901, found that the rate of oxidation of mixtures of sulfuric acid and potassium iodide increased proportionally with the concentration of the

sulfuric acid in light, but not in darkness, provided the concentration of iodine did not exceed one gram per liter. The accelerating influence of light was most marked in dilute solutions. When sulfuric acid was replaced by hydrochloric acid, the reaction was twice as rapid, while phosphoric acid had only a slight accelerating influence on the rate of decomposition in light.

J. Plotnikoff (184) studied the oxidation of the hydriodic acid present in a mixture charged with oxygen, of solutions of potassium iodide and hydrochloric acid. The oxidation proceeded at a measurable rate in darkness and was markedly accelerated by light of the spectral region around 4360 Angstrom units. It was concluded that the photochemical oxidation was proportional to the concentration of oxygen, to the two-thirds power of the concentration of potassium iodide and to the four-thirds power of the concentration of hydrochloric acid. The reaction in darkness was accelerated by a cupric salt or a mixture of ferric and cupric salts; manganese and lead salts exerted no appreciable catalytic action; the catalytic effect of nitrous acid was very marked even if the solution contained the equivalent of only 0.00000006 N nitrous acid. Additions of uranyl sulfite retarded the velocity of the reaction in light as did starch, eosin, and cupric sulfite; in the dark, the latter compound accelerated the

decomposition.

In a later article, Plotnikov (185) repeated the work outlined above and found that if very pure chemicals were used, the rate was always proportional to the two-thirds power of the concentration of hydrochloric acid both in the light and in the dark. He found that the ferrous ion accelerates the change slightly and that the temperature coefficient for the reaction was 2.07 in the dark and 1.39 in the light.

In 1908, Creighton and Mackenzie (186) found that under some conditions the decomposition of hydriodic acid was accelerated by the influence of radium but that at room temperature in the absence of oxygen, neither sunlight nor radium caused decomposition of the dilute hydriodic acid solutions.

Kailan (187), in 1913, reported that slightly or strongly acid solutions of manganese, calcium, strontium and barium iodides are decomposed by X-rays. The decomposition increased with increasing concentrations. There was no connection between the molecular weight of the iodide and the rate of decomposition.

Husa and Shattuck (188) found that the rate of decomposition of hydriodic acid was increased by the

following factors: exposure to air, exposure to light, increase in temperature and increase in concentration. The effect of various iodides in 0.5 M concentration upon the rate of decomposition of 0.1 N hydriodic acid in the dark was as follows: marked acceleration, Fe and Mn; appreciable acceleration, Na, Sr, NH_4; slight acceleration, Ca, K, Li; slight retardation, Mg, Cd, Zn; marked retardation, Ba. Only FeI_2 and MnI_2 had any effect on the rate of decomposition of 0.1 N HI when present in concentrations of 0.1 M, 0.01 M or 0.001 M; this effect was attributed to a specific catalytic effect of Fe and Mn ions. The effect of iodides in general was explained on the basis of the increased concentration of HI molecules brought about by the common ion effect of the iodides. It was stated that on the basis of this hypothesis, iodides which are only slightly ionized would have little effect and that the formation of double iodides such as $2\ HI \cdot CdI_2$ or H_2CdI_4 would tend to withdraw some HI molecules and by thus lowering their concentration would lower the rate of decomposition; the experimental results were consistent with this explanation.

Husa and Magid (189) measured the effect of various iodides upon the rate of decomposition of 0.1 N hydriodic acid, and found that when present in half normal concentration, ferrous, manganese and strontium iodides caused

marked acceleration; sodium, potassium and lithium iodides caused appreciable acceleration; magnesium, calcium and ammonium iodides caused slight acceleration; slight retardation was caused by zinc and cadmium iodides; marked retardation was caused by barium and mercuric iodides. It was found that in solutions of constant pH, an increase in the iodide concentration increases the rate of decomposition of hydriodic acid, and with constant iodide concentration, an increase in hydrogen ion concentration increases the rate of decomposition. The rate of decomposition is increased more by HCl than by H_2SO_4. The effect of various salts on the rate of decomposition of hydriodic acid was measured with the following results: marked acceleration, $NiCl_2$, $FeCl_2$ and $CoSO_4$; no effect, NH_4Cl, LiCl and NaCl; slight retardation, $MnSO_4$, $MgCl_2$, $SrCl_2$, $BaCl_2$, $ZnCl_2$, $CaCl_2$ and KCl; marked retardation, $Al_2(SO_4)_3$ and $CdCl_2$. It was concluded that salts that have no ion in common with hydriodic acid, but have a marked tendency to increase the rate of decomposition of hydriodic acid, may be regarded as having a cation which has a specific catalytic effect on the oxidation of hydriodic acid. Ni , Fe and Co were regarded as having a specific catalytic effect. The retarding influence of certain salts was correlated with the known tendency toward formation of complex ions, thus reducing the concentration

of iodide ions and HI molecules.

4. Carbohydrates.

Glucose or dextrose ($C_6H_{12}O_6$), a monosaccharide, exhibits the characteristic properties of the sugars. Syrupy or commercial glucose commonly contains sulfites and other impurities. On warming with alkali, the monosaccharides give yellowish-brown solutions and finally resinify. Glucose upon oxidation in acid media yields d-gluconic acid and finally d-saccharic acid. Nef (190) has shown that glucose in alkaline solution oxidizes spontaneously in the presence of air with the formation of from 93 to 116 other substances. It has also been shown (191) that glucose is oxidized by bleaching powder. Goebel (192) reviewed the work of Willstätter and Schudel (193) who had described a method for the determination of sugars involving the principle of Romijn (194) that hexoaldoses may be quantitatively oxidized to the corresponding acid in the presence of iodine in alkaline solution:

$$R\text{-}C\begin{matrix}O\\ \diagdown\\ H\end{matrix} + I_2 + 2\ NaOH \longrightarrow RCOONa + 2\ NaI + 2\ H_2O\ .$$

l-Fructose or levulose occurs together with glucose in honey etc. It is a ketonic sugar, less soluble in water than glucose, m.p. 95° C. It can be reduced to a

mixture of d-mannitol and d-sorbitol. Oxidation breaks the molecule to give d-erythronic acid, $CH_2OH(CHOH)_2COOH$ and glycollic acid $CH_2(OH)COOH$.

Sucrose, the anhydride of fructose and glucose, has been shown to be readily inverted when in solution (195) probably due to the action of B. Penicillium. Inversion is catalyzed by the presence of salts of heavy metals, particularly iron (196), and by hydrogen or hydroxyl ions (197); thus organic acids invert sucrose more slowly than mineral acids (198). Zisch (199) has stated that in solutions of pH 6.8 to pH 6.9, the inversion is three times as rapid as in solutions having a pH of 7.2 and Spoehr (200), (201), has shown that the ferrous ion exerts an accelerating effect upon this inversion. The velocity of inversion of sucrose in mixed solvents has been studied (202) and it was found that in mixtures of water with methyl alcohol, ethyl alcohol, isopropyl alcohol, glycol, glycerin and methyl acetate, the rate is first accelerated and then retarded as the percentage of non-electrolyte is increased. In each case the composition-velocity constant curve passes through minima and maxima, the results being attributed to hydration, lowering of the dielectric constant and viscosity. Upon heating to about 180° C., sucrose forms a brown product known as caramel which is a mixture of the decomposition products

of sugar and usually contains aldehydes (203).

That sugar solutions possess the property of peptizing or preventing the precipitation of ferric hydroxide has long been known. Scoville (204) stated that glycerin, sugar, honey and gums are effective peptizing agents but that invert sugar is seven times as effective in holding up ferric hydroxide as is sucrose. Graham (205), reported that ferric hydroxide is readily peptized in alkaline solutions of organic hydroxy compounds and Powis (206) stated that ferric hydroxide sols, although commonly regarded as containing a positively charged colloid, may contain a negatively charged colloid if the sol is prepared in alkaline solution. Mehrota and Sen (207) studied the peptizing power of sucrose, dextrose, levulose and lactose with respect to ferric hydroxide. They found that the limit of peptizing power differed for each sugar and that in contrast to most metallic hydroxides, ferric hydroxide can be peptized in acid but not in neutral solution.

Sen (208) found that ferric hydroxide is peptized by glycerin but in general non-electrolytes do not function as peptizing agents in the usual sense of the term. He stated that ferric hydroxide sols are positively charged if hydroxyl ions are not in excess but are negatively charged in basic solutions.

Hakomari (209) concluded that the non-precipitation of iron in hydroxy-acid solutions is due partly to the formation of a complex between the iron and the acid.

Bancroft (210) stated a theory accounting for peptization which was based on adsorption phenomena. He thought that any substance adsorbing a second substance has its surface tension lowered and tends toward disintegration.

Bachmann (211) investigated the products obtained by adding sodium hydroxide to iron solutions in the presence of glycerol, sucrose and other compounds and concluded that the metal is present partially as a colloid and partially as a crystalloid complex.

5. Oxidation-Reduction Potentials.

The potential established between ferrous ions and any other pole is extremely difficult to measure. Both the hydrogen electrode and the quinhydrone electrode precipitate metallic iron from solution with the result that readings of electromotive force are not valid. In practice, these determinations may be made by the use of glass electrodes. Michaelis (212) observed that the E.M.F. values were also complicated by the formation of complex salts but succeeded in obtaining reproducible

values by the addition of an electronegative dye after reduction with colloidal palladium and hydrogen.

A consideration of the normal electrode potentials, i.e. the potential established by the ion in question against a solution one molar with respect to that ion, of several substances concerned, shows the following (213) :

Table 2.

Normal Electrode Potentials.

System	Electrode reaction	Potential[1]
$(Fe^{+++}, Fe^{++})Pt$	$Fe^{+++} + e = Fe^{++}$	+0.7477
(Fe^{++}, Fe)	$Fe^{++} + 2\ e = Fe$	-0.441
(Fe^{+++}, Fe)	$Fe^{+++} + 3\ e = Fe$	-0.04
$(\frac{1}{2} I_2, I^-)Pt$	$\frac{1}{2} I_2 + e = I^-$	+0.5345
$(OH^-, O_2)Pt$	$\frac{1}{2} O_2 + e = OH^-$	+0.3956

As indicated in Table 2, oxygen will first oxidize iron to the ferrous state, then iodide ion to free iodine and lastly, ferrous iron to the ferric state.

It is possible to calculate the possibility of

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1. The negative sign is here used to indicate that the electrode is negative to a solution of its ions at unit activity when the electrode is connected to a normal hydrogen electrode.

oxidizing ferrous ion to ferric ion with iodine by determining the potential of a cell for which the reaction is represented:

$$Fe^{++} + \tfrac{1}{2} I_2 \longrightarrow Fe^{+++} + I^- \ .$$

Such a cell would be:

$$Pt(Fe^{+++}, Fe^{++}) \,\|\, I^-, I_2 \quad \text{or,}$$
$$-0.7477 + 0.5345 = -0.2132 \ ,$$

and the negative value obtained indicates that the reaction will not go spontaneously.

Noyes (214) states that the values as determined for normal electrode potentials may be reduced to the corresponding values for other concentrations by adding for each tenfold decrease in the concentration of any ion present in the oxidized state 0.06, 0.03, or 0.02 according as the difference in valence of the two states is unity, two or three respectively, and subtracting the same quantities from the given values for each tenfold decrease in the concentration of any ion present in the reduced state.

Applying this information to the case of Syrup of Ferrous Iodide which is approximately 0.236 molar with respect to ferrous iodide, and assuming the ionization

to occur:

$$FeI_2 \rightleftharpoons Fe^{++} + 2\ I^- \quad ,$$

it is evident that each mol of ferrous iodide furnishes one mol of ferrous ions and two mols of iodide ions, and calculating according to Noyes, we obtain the following values, valid for the actual concentration of ferrous iodide in the U.S.P. syrup:

$$(Fe^{+++}, Fe^{++})Pt = 0.7304$$
$$(I^-, \tfrac{1}{2} I_2)Pt = 0.4999$$

Thus it appears that in Syrup of Ferrous Iodide, iodide ion would be oxidized to free iodine before ferrous iron is changed to the ferric state.

6. The Action of Light.

The infra red region of the spectrum was discovered by Herschel in 1800 and the action of ultra violet light on silver salts was noted by Ritter in 1801. Grotthuss, in 1818, enunciated his "Photochemical Absorption Law" stating that only the rays that are absorbed are effective in producing chemical change and Einstein, in 1912, stated that in a photochemical reation, one quantum of active light is absorbed per molecule of absorbing and reacting

substance, although in most cases the quantum yield greatly exceeds this theoretical value (215).

The action of light affects many reactions including those of the decomposition of iron compounds and hydriodic acid. It has been shown that the photochemical decomposition of HI in the gas phase:

$$2\ HI \rightarrow H_2 + I_2$$

is extremely light sensitive and affected by the concentration of acid. It has also been shown that quinine accelerates the reaction by "photosensitization" (216).

Winther and Oxholt-Howe (217) have shown that the decomposition of ferric citrate for short wave lengths has a reaction velocity which is approximately constant. The quantum sensitivity, however is greater than unity, thus showing a catalytic activity.

Scoville (218) stated that ferric citrate is readily reduced to ferrous compounds by the action of light.

Burt (219) observed that sunlight reduced ferric salts to the ferrous condition in the presence of citric acid and that the citric acid was decomposed, a result in accord with other investigators (220), (221), (222), (223), (224), (225).

Fry and Gerwe (226) advanced a mechanism for the decomposition of ferric citrate solutions in the presence of sunlight and reviewed the work of Eder (227) and Vries (228) who verified the reduction of ferric to ferrous salts by the action of light, in the presence of citric, tartaric, malic and oxalic acids.

Neuberg (229) made extensive studies of the action of light on ferric and uranic salts.

Rideal and Williams (230) among others, investigated the action of light on ferrous-ferric, iodine-iodide equilibria. They investigated the reaction:

$$2\ Fe^{+++} + 2\ I^- \underset{\text{light}}{\overset{\text{dark}}{\rightleftharpoons}} 2\ Fe^{++} + I_2$$

and found it to be photosensitive, fulfilling the Einstein Law of Photoequivalence. The sensitive constituent was stated to be iodine, the iron salts and the iodide ion being inactive. The reaction was found to be sensitive to both ultra-violet and visible light with a maximum at 5800 Angstrom units. The temperature coefficient of the liberation of iodine in the dark was found to be 2.713 and that of the photochemical reaction was 1.17. The mechanism of this reaction was explained by Wagner (231), and further investigations were made by Sasoki (232) and

Brönsted and Pederson (233).

7. Auto-oxidation and Antioxidants.

Berthollet (234), in 1797, observed that traces of the vapors of sulfur compounds prevented the luminescence of phosphorous in a dilute atmosphere of oxygen. Since that time, the discovery of substances which retarded the spontaneous oxidation of other chemicals has been numerous although the mechanism of their action is still doubtful.

Englis and Bach (235) first believed that peroxide formation occurred in all cases of auto-oxidation, but this theory was not sufficiently broad in its concepts and was followed by the dehydrogenation theory of auto-oxidation. Luther (236) thought that anti-oxidants acted by destroying positive catalysts always present, while others (237) believed the mutual destruction of peroxides formed was accomplished by interaction of the original active peroxide of the auto-oxidizable substance and the inhibiting agent. At present, the following theory is generally accepted: all antioxidants possess molecular valence electrons, and an exchange of energy therefore, between the inhibitor and the "dative" peroxide resulting in partial activation of the former is inevitable to inhibitory action; this inhibition however, takes place only if the inhibitor is in "resonance" with the auto-

oxidizable substance. Activated molecules of the inhibitor can then be either oxidized by organic peroxides or by free oxygen or can combine with the active auto-oxidant molecules forming unstable complexes which may decompose to the original inhibitor molecules.

Milas (238) characterizes auto-oxidation reactions as exothermic in nature and usually displaying a period of induction; in other words the rate of reaction increases until a maximum is reached.

Positive catalysts for auto-oxidations may be divided into three classes: (a) organic peroxides and ozonides, (b) inorganic compounds such as the metals, salts and complex ions, (c) radiation and high frequency super-sonic sound waves.

Wieland and Franke (239) studied the auto-oxidation of organic compounds in the presence of ferrous and ferric iron and found that ferrous iron was the best catalyst.

Berl and Winnacker showed that colloidal iron is a negative catalyst in the auto-oxidation of benzaldehyde (240). The same authors showed that ferrous iodide inhibits the auto-oxidation of benzaldehyde and acrolein although they ascribed the negative catalysis to the liberation of free iodine. It was concluded that the

catalytic action of iron is variable in sign and intensity depending upon the catalyst used and the character of the auto-oxidant.

Manchot (241) found that ferric hydroxide inhibits the oxidation of sodium sulfite in slightly acid solution. He believed that in cases of this kind, oxygen was activated or inactivated by the formation of an intermediate peroxide of iron:

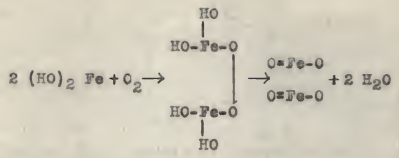
$$Fe + O_2 \rightarrow FeO_2 \ ,$$

but later (242) stated that the peroxide formed was in reality Fe_2O_5.

Baudisch and Welo (243) agreed with Manchot's view but believed that the intermediate peroxide formed was FeO_3 in combination as a complex with water:

$$\left[\underset{O_2}{FeO_2}(H_2O)_5\right](OH)_2 \ .$$

Milas (244) stated that the best explanation is that given by Hale (245) and which may be summarized as follows: ferrous iron by virtue of its lone valence electron combines with oxygen like a free radical, comparable to triphenyl methyl:



Lamb and Elder (246) showed that the auto-oxidation of ferrous sulfate was inhibited by the presence of certain narcotics and accelerated by copper salts, cocoanut charcoal etc.

Schmitt, Johnson and Olson (247) found that ultrasonic waves of high frequency acted as positive catalysts for many auto-oxidations.

In general, it may be said that anti-oxidants are substances which can themselves be oxidized but which prevent or inhibit the auto-oxidation of some other substance.

8. Theories of Decomposition.

Phillips (248) stated that in his opinion the first step in the decomposition of solutions of ferrous iodide is the formation of ferrous oxide and hydriodic acid from decomposition by water. The ferrous oxide however, changes rapidly under the influence of atmospheric oxygen to ferric oxide and precipitates, while hydriodic acid

is set free. The hydriodic acid is then decomposed by air and free iodine is liberated. This explanation, according to Phillips, accounts for the acidity of the solution from the moment of precipitation. The final black color of the preparation was thought to be due to the formation of a "persalt" of iron.

Fruckhinger (249) found that the evaporation of solutions of ferrous iodide containing sugar gave a black residue. All tests, however, showed that iron was still in the ferrous state but that sugar would no longer ferment and thus had been converted into a brown "humic"[1] substance.

Maisch (27) believed that both light and oxygen effected decomposition of ferrous iodide preparations, liberating iodine and hydrated oxides of iron.

Meyer (251) also thought that the acidity was due to the formation of hydriodic acid in the syrup although he made no reference to Phillip's work.

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1. Chemically, humin or "humic" substances are considered to be dark colored products closely related to the melanins. They are obtained by acid hydrolysis of proteins although little is known of their properties (250).

Hammer (51) stated that the decomposition was due to the conversion of ferrous iodide into ferric oxide by atmospheric oxygen.

Tschirner (252) however, believed the acid reaction of the syrup to be characteristic of iron compounds. He thought the formation of ferric iodide to be extremely doubtful since no positive test for ferric iron could be obtained either after iodine appeared in the solution or in a solution made by dissolving ferric hydroxide in hydriodic acid.

Mylius (253) stated that by the action of oxygen and water on ferrous iodide, a basic ferric iodide analagous to basic ferric chloride would be formed provided such a compound existed. He gives, however, the following reaction as accounting for the decomposition:

$$2\ FeI_2 + O_3 + (H_2O)_3 \longrightarrow Fe_2(OH)_6 + I_4\ ,$$

iodine and ferric oxyhydrate being liberated. The bleaching action of sunlight was recognized and accounted for by assuming that sugar in the presence of light, reduces the "oxyhydrates" and free iodine again combines to form ferrous iodide:

$$Fe_2(OH)_6 + I_4 + H_6 \longrightarrow (FeI_2)_2 + (H_2O)_6\ ,$$

the hydrogen in the above reaction being supposedly obtained from the sugar molecule thus forming a free acid, probably gluconic.

Wearn (254) investigated the darkening which appears in syrups containing ferric phosphate. He placed both a solution and a syrup in sunlight and in darkness and found that in either case, ferrous iron appeared in the preparation in conjunction with the appearance of discoloration. He concluded that sugar was thus excluded as a factor in the darkening process.

Salzer (255) noted that the syrup made according to the German Pharmacopoeia III soon acquired a reddish-yellow color, and at first thought this to be due to the formation of ferric oxy-iodide. He found, however, that the cause lay in the amylo-dextrin content of filter paper which is dissolved during the filtration by ferrous iodide solutions. Upon decomposition according to the following reaction:

$$FeI_2 + 2\ H_2O + O \longrightarrow Fe(OH)_3 + I + HI \quad ,$$

iodized starch is formed and when this compound is mixed with hydrated ferrous oxide, the discoloration appears.

Woltersdorff and Richtmann (256) found that the action of light played no part in the preservation of Syrup of

Ferrous Iodide since all discolored samples which were restored by sunlight were also restored by heating in the dark on a water bath. They concluded that the heat of the sun was in reality the preserving agent.

Haussmann (257) stated that the permanent dark coloration appearing after a time in Syrup of Ferrous Iodide was due to the decomposition of levulose formed by the hydrolysis of sucrose, and Jungflesh and Grembart (258) and D'Arcet (259) have shown that levulose decomposes to form a mixture of formic and levulinic acids together with certain coloring matters called humin.

Haussmann (260), in a later article, stated that the discoloration in the syrup was due to caramelization and in exceptional cases only to oxidation of the salt. He added that moreover, ferrous iodide is not the only iron salt which causes darkening in syrups, ferrous sulfate preparations also turning dark in four to six months, especially if heat is applied.

Kimmich (261) worked on galenicals containing iron, notably those containing phosphate, pyrophosphate and citrochloride of iron and found that the less sugar contained, the slower is the darkening process. Glycerin was found to retard this discoloration.

Pamiflov and Petin (262), working on the kinetics of inductive processes, investigated the effect of oxides of iron on the liberation of iodine from iodides by the oxidation of the salt with hydrogen peroxide. They found that not only the initial velocity but also the nature of the dependence of iron concentration and acidity vary with the state of oxidation of the iron present. In neutral or faintly acid media, the reaction is accelerated more by ferrous oxide than by ferric oxide at low concentrations. The mechanism suggested is based on the spontaneous oxidation of ferrous oxide and the retarding influence exerted by acidity is related to the great stability of ferrous ions in acid solution.

Krantz' (130) work, in which he ascribed the decomposition to a combination of oxidation and caramelization has already been referred to (See page 130 ff).

Bentley (263) and Bentley and Driver (264) stated that decomposition proceeds according to the following reaction:

$$2\ FeI_2 + O_2 \longrightarrow 2\ FeOI + I_2 \quad ,$$

wherein the formation of basic ferric iodide is presumed although no proof was offered for this supposition.

Schissele (265) stated that Syrup of Ferrous Iodide

turns brown in the dark but not because of free iodine, and that exposure to sunlight tends to remove the discoloration. Horn (266) and Dunning (267) have reported similar observations as regards the appearance of color.

Sadtler and Coblentz (268), in their textbook, state under the influence of water and oxygen from the atmosphere, ferrous iodide reacts to form ferric hydroxide, iodine and hydriodic acid as follows:

$$2\ FeI_2 + 2\ H_2O + \tfrac{1}{2}\ O_2 \longrightarrow Fe(OH)_3 + I + HI \quad (1)\ ,$$

but that in the presence of hypophosphorous acid, the iodine is converted to hydriodic acid, thus preserving the syrup until no more hypophosphorous acid is present in solution:

$$H_3PO_2 + 2\ I_2 + 2\ H_2O \longrightarrow H_3PO_4 + 4\ HI \quad (2)\ ,$$

and it appears that at present, this is the generally accepted mechanism of the reaction.

Arny and co-workers (127), (128), (129) concluded from their experiments (See pages 34-37) that the cause of permanent discoloration was caramelization due to the presence of hypophosphorous acid.

IV. EXPERIMENTAL PART.

1. Scope of Investigation.

A review of the literature concerning Syrup of Ferrous Iodide emphasizes the disagreement and controversy regarding practically every phase of this preparation since its introduction in 1824. Certain causes of these contradictions are, however, inherently due to the character of the preparation itself, while others appear to be due to the failure of investigators to specify the conditions under which they worked; moreover, the two distinct stages of decomposition were frequently confused and many misleading statements have been made with nothing more than supposition as a basis.

In order to evaluate previous work, particularly that upon which much disagreement exists, a careful and extensive series of experiments was performed dealing with the manufacture, decomposition and preservation of Syrup of Ferrous Iodide. Gravimetric and volumetric assays were performed upon the reaction mixture and finished product; the extent of hydrolysis and the hydrolytic equilibria were obtained; the rate of decomposition was measured in terms of the monomolecular reaction velocity constant, and comparisons made with similar rates of decomposition for solutions containing various preservatives; the rate of

reaction of various preservatives with iodine was measured; the action of light was determined in quantitative terms for various spectrum bands; and a thorough study was carried out upon the effect of preservatives under actual practical conditions.

2. Analytical Methods.

Apparatus and Reagents. In the present investigation, numerous analyses became necessary. For this purpose, all burettes and pipettes were carefully calibrated against a set of weights previously calibrated according to the method of Jenkins and DuMez (269). Delivery from the glassware used was within the time limits specified by the Bureau of Standards (270).

Standard solutions were prepared and standardized as follows: N sulfuric acid standardized against Baker's anhydrous C.P. sodium carbonate previously heated for 30 minutes over a low Bunsen flame and allowed to cool in a dessicator (271); 0.01 N iodine solution was prepared by dissolving the proper weight of Merck's Reagent iodine in chloride-free distilled water containing 18 Gm. per liter of Merck's Reagent KI (272); 0.01 N and 0.03 N sodium thiosulfate solutions were standardized against 0.01 N iodine and against 0.1 N potassium dichromate solution

previously prepared by weight from Mallinckrodt's C.P. potassium dichromate (273); Merck's C.P. silver nitrate was used in the preparation of 0.1 N solution in chloride-free water and standardized against Merck's Reagent sodium chloride (274); 0.1 N potassium thiocyanate solution was prepared from Baker and Adamson's (General Chemical Co.) Reagent grade chemical and standardized against 0.1 N silver nitrate solution (275); Mallinckrodt's U.S.P. potassium permanganate was used in the preparation of the 0.1 N solution in water redistilled from 0.1% permanganate solution, and standardized against 0.01 N sodium thiosulfate solution and Merck's Reagent ferrous ammonium sulfate (Mohr's salt).

Starch T.S. prepared from Baker's analyzed C.P. potato starch and methylene blue solution (276) prepared from Merck's U.S.P. chemical were used as indicators for the iodometric determinations. Ferric ammonium sulfate T.S., prepared from Baker's C.P. analyzed chemical, was used as the indicator in total iodide determinations.

Determination of Ferrous Iron. Of the many methods available for the determination of ferrous iron, it is generally agreed that the permanganate method is the most expeditious and yet sufficiently accurate for all practical purposes. If, however, we attempt to determine ferrous iron in ferrous iodide preparations by titration with perman-

ganate, the iodine liberated by oxidation colors the solution so strongly that the delicate end-point is completely masked. The dichromate method for the determination of ferrous iron is more satisfactory in this particular case than is the permanganate method. It has the great disadvantage, however, of requiring an external indicator with consequent loss of accuracy and increase in difficulties of manipulation.

In order to determine accurately and rapidly, the ferrous iron content of the ferrous iodide preparations used in this investigation, the following method of assay was developed: To 5 cc. of a solution of ferrous iodide, accurately measured, and contained in an Erlenmeyer flask, add about 25 cc. of distilled water, 10 cc. of Diluted Sulfuric Acid and an excess (about 5 cc.) of an approximately half-normal silver nitrate solution. Titrate the solution with 0.1 N potassium permanganate solution until a permanent pink coloration remains after shaking the liquid.

This method of assay is rapid and accurate and furnishes a well defined end-point. The precipitate of iodide, originally clouding the liquid, flocculates markedly as permanganate is added, until, as the end-point is approached, it collects rapidly in the bottom of the flask leaving a clear supernatant liquid.

In some cases, a darkening of the solution occurs

either during the titration with permanganate or before titration has begun. In the former case, the coloration is due to liberation of free iodine, thus indicating that silver nitrate has not been added in excess; this can be remedied by the addition of another portion of silver nitrate solution. In the latter instance, no treatment is necessary, as the coloration fades rapidly with the addition of permanganate and at the end point, the solution is practically colorless.

Determination of Total Iodide. The U.S.P. X directs that Syrup of Ferrous Iodide be assayed by determination of the amount of silver nitrate volumetric solution required to entirely precipitate the iodide. The determination is made by adding an excess of silver nitrate volumetric solution to the syrup, warming to insure complete reaction, and titrating the excess of silver nitrate with 0.1 N potassium thiocyanate solution, ferric alum being used as the indicator.

Verification of Method. In order to verify the method outlined above for the determination of ferrous iron, a number of titrations were performed. Ferrous ammonium sulfate (Mohr's salt) was used in one series of standards and a solution of ferrous iodide in another. Ferric iron was added as ferric ammonium sulfate in the case of Mohr's

salt and as ferric chloride in the case of solution of ferrous iodide. Iodine was added as an 0.01 N solution of the halogen. The various iodides were added as the solid crystalline salts. In the case of titrations conducted using Mohr's salt as a standard, results were calculated simply as the factor for the permanganate and the relative constancy of this factor in all cases offers ample evidence of the accuracy of the method employed. On the other hand, the ferrous iodide samples are calculated as grams per liter from the factor as determined for permanganate from ferrous ammonium sulfate. No further experimental work was considered necessary to establish the validity of this method of assay since no fundamental difference exists between it and the usual permanganate method. Data follow:

Table 3.

Ferrous Ammonium Sulfate Titrations.

Gm. Mohr's salt	Cc. permanganate	Factor
0.21840	5.85	0.09518
0.21349	5.72	0.09517
0.20760	5.56	0.09521
0.21040	5.64	0.09513
0.20930	5.61	0.09513

Since each gram of ferrous ammonium sulfate contains 0.14239 grams of ferrous iron, factors in the above table

were calculated as follows:

$$\frac{\text{Wt. of sample} \times 0.14239}{0.005584 \times \text{cc. } KMnO_4} = \text{Factor}$$

Table 4.

Solution of Ferrous Iodide Titrations.

Cc.Sol. of FeI_2	Cc. $KMnO_4$	Ferrous iron Grams per L.
5	11.80	12.54
5	11.80	12.54
10	23.60	12.54

As indicated in Table 4, the content of ferrous iodide assays 12.54 grams per liter in each of three titrations. An assay of the same solution by the U.S.P. X method for total iodide shows that the solution should contain 12.543 grams per liter of the salt.

Table 5.

Effect of Iodine upon the Determination of Ferrous Iron.

Gm. Mohr's salt.	Cc. Sol. FeI_2	Cc. .01 N Iodine	Cc. $KMnO_4$	Factor	Fe Gm./L.
0.19940		2	5.34	.09522	
0.30460		5	8.16	.09518	
0.29240		10	7.83	.09522	
	5	2	11.78		12.52
	5	5	11.81		12.55
	5	10	11.79		12.53

It was concluded from these data that the presence of free iodine and iodide ion had no appreciable effect upon determination of the factor for permanganate or the quantity of ferrous iron in grams per liter.

Table 6.

Effect of Excess Iodide Ion.

Gm. Mohr's salt.	Cc. Sol. FeI_2	Gm. Iodide	Cc. $KMnO_4$	Factor	Ferrous iron Grams per L.
0.17690		0.2 KI	4.74	0.09517	
0.20320		0.5 KI	5.44	0.09525	
0.26410		1.0 KI	7.08	0.09512	
0.35381		0.2 LiI	9.48	0.09517	
0.30610		0.5 LiI	8.20	0.09519	
0.34230		1.0 LiI	9.17	0.09518	
	5	0.5 KI	11.81		12.55
	5	1.0 KI	11.79		12.53
	5	2.0 KI	11.80		12.54

Table 6 indicates that excess iodide ion has no effect upon the validity of the method of assay used.

Table 7.

Effect of Ferric Iron.

Gm. Mohr's salt.	Cc. Sol. FeI_2	Gm. KI	Gm. Ferric alum.	Cc. $KMnO_4$	Factor	Ferrous iron Gm./L.
0.22500		0.2	0.2	6.03	.09514	
0.34280		0.2	0.5	9.18	.09522	
0.27630		0.2	1.0	7.40	.09521	
	5		0.1	11.82		12.57
	5		0.3	11.80		12.54
	5		0.5	11.79		12.53

It was concluded from the results in Table 7, that the presence of neither ferric iron nor a combination of ferric iron and iodide ion in excess had any effect upon the method of assay.

Table 8.

Effect of Ferric Iron, Iodine and Iodide Ion.

Cc. Sol. FeI_2	Gm. Ferric alum.	Gm. KI	Cc. .01 N I_2	Cc. $KMnO_4$	Ferrous iron Gm./L.
5	0.2	0.2	2.0	11.81	12.55
5	0.5	0.5	5.0	11.80	12.54
5	1.0	1.0	10.0	11.80	12.54

It was concluded from the results in Table 8, that the method of assay used was not affected by the presence of a

combination of free iodine, excess iodide ion and ferric iron.

Table 9.

Effect of Dextrose.

Gm. Mohr's salt.	Gm. Dextrose.	Theoretical Cc. $KMnO_4$ required.	Cc. $KMnO_4$ used.
0.12589	1.0	3.373	11 plus
0.23460	1.0	6.286	25 plus

Since the number of cc. of potassium permanganate solution used exceeded the theoretical quantity necessary to oxidize all the iron present, it was concluded from these data that this method of assay is not valid for solutions containing reducing sugars.

3. The Manufacture of Ferrous Iodide.

Numerous methods have been given in the literature for the preparation of ferrous iodide both in the solid state and in solution. The present revision of the United States Pharmacopoeia directs that the salt be prepared in aqueous solution by direct union between iron and iodine, heating the flask to boiling at the expiration of the reaction in order to drive the reaction to completion and volatilize any gaseous compounds of sulfur or phosphorus which might be formed as a result of impurities in the iron (277). Various authors (111), (116), have stated that the reaction

carried out in this manner fails, despite its apparent simplicity, to go smoothly and evenly to completion and that in no two instances does the reaction progress with the same speed and vigor. Bohrisch (116) has even suggested that a catalyst in the form of an iron spatula or coil of iron wire be placed in the liquid during the reaction, a statement which is obviously not in accordance with our criteria of catalytic agents.

In this investigation, solutions of ferrous iodide were prepared by the following methods: solution of the solid salt in water; reaction between iron (card teeth) and U.S.P. iodine[1] in water; reaction between iron (card teeth) and C.P. iodine[2] in water; reaction between iron (card teeth) and Reagent iodine[3] in water; reaction between Reagent iron wire[4] and U.S.P. iodine in water; reaction between Reagent iron wire and C.P. iodine in water; reaction between Reagent iron wire and Reagent iodine in water; metathesis between Merck's Reagent ferrous sulfate and Mallinckrodt's barium iodide; metathesis between U.S.P. mercurous iodide and Merck's Reagent ferrous sulfate in water. Attempts were

1. All U.S.P. iodine used in this work was Mallinckrodt's.
2. Merck's C.P. iodine was used throughout.
3. Merck's Reagent iodine was used throughout.
4. Merck's Reagent Iron Wire was used throughout.

also made to prepare samples of the solution with alcohol, benzene and ether as the reaction solvents. In the case of benzene and ether no reaction could be observed while the reaction does not go to completion under ordinary conditions in alcohol.

The solid salt used in the preparation of the solution mentioned above was prepared as follows. A concentrated aqueous solution of ferrous iodide was evaporated under reduced pressure in an atmosphere of hydrogen until of syrupy consistency, removed to an evaporating dish and quickly evaporated to dryness over a low flame. The residue was then rubbed in a mortar with successive portions of petroleum ether until no color was imparted to the liquid. The residue was taken up in the smallest possible quantity of alcohol and evaporated in a dessicator. The solid salt appeared as an amorphous red-brown powder deliquescing rapidly in air to a red-brown liquid. It was completely soluble in water.

In the preparation of ferrous iodide by double decomposition it is essential that all ingredients used be of high purity since traces of impurity tend to liberate free iodine in the reaction mixture.

Variations in Reaction Time. In order to investigate

previous statements of the variability of the reaction, a series of experiments was carried out in each of which weighed quantities of the reactants were placed in a beaker which in turn was immersed in a large water bath and both beaker and bath fitted with mechanical stirrers. Thermometers were immersed in both the reaction vessel and the bath. Efficient stirring was provided in every case and the temperature remained practically constant throughout the progress of the reaction. It is significant that the products were invariably colorless and free from iodine, the end-point being taken as the time when the mixture gave no blue color with starch T.S.

Table 10.

Reaction Time of Iron and Iodine.

No.	Form of: Iron	Iodine	Time[1]	Temperature	Residue[2]
1	Card teeth	U.S.P.	1 hr. 45'	22° C.	Black
2	Card teeth	U.S.P.	1 hr. 45'	21° C.	Black
3	Card teeth	U.S.P.	1 hr. 35'	23° C.	Black
4	Card teeth	U.S.P.	1 hr. 50'	26° C.	Black
5	Card teeth	U.S.P.	1 hr. 40'	22° C.	Black

1. The time listed is accurate only to the nearest 5 minute interval.
2. The term residue refers to the insoluble matter remaining on the paper after filtration.

Table 10 - cont.

Reaction Time of Iron and Iodine.

No.	Form of: Iron	Iodine	Time[1]	Temperature	Residue[2]
6	Card teeth	C.P.	1 hr. 35'	23° C.	Black
7	Card teeth	Reagent	1 hr. 40'	24° C.	Black
8	Reagent	U.S.P.	1 hr. 50'	22° C.	Brown
9	Reagent	C.P.	1 hr. 25'	23° C.	Brown
10	Reagent	Reagent	1 hr. 35'	22° C.	Brown

The results shown in this tabulation indicate that the reaction under these conditions, goes to completion with approximately the same speed in every instance, regardless of the degree of purity of the chemicals used.

It was originally thought that the carbon content of card teeth might accelerate the reaction rate catalytically. The addition of finely divided carbon to the reaction mixture, however, failed to alter the data as obtained in Table 10.

It was concluded that the manufacture of ferrous iodide by direct union of the elements in aqueous solution progresses smoothly and evenly to completion under uniform conditions of temperature and agitation.

Manufacture by Direct Union. Samples were next prepared by direct union and double decomposition, the pH

values being noted in each case for use in later work. Ferrous iron in these preparations was determined by the method previously outlined and iodide determinations were carried out by the U.S.P. X method of assay. The pH of the distilled water used throughout was 5.7.

A. Samples prepared from card teeth.[1]

1. Three samples of two liters each were prepared from card teeth and U.S.P. iodine. The reaction was carried out as prescribed for Syrup of Ferrous Iodide, boiling the reaction mixture at the expiration of the reaction. During the progress of the reaction, one of these samples was allowed to remain at a temperature near the point of volatilization of the iodine; the other two were cooled by immersion in running water. Analyses showed:

Sample	Ferrous iron mols/L.	Iodide mols/L.	pH	Indicator
Heat not removed	0.2314	0.2256	3.2	La Motte yellow
			3.3	bromphenol blue
Heat removed	0.2294	0.2248	3.2	La Motte yellow
			3.3	bromphenol blue
Heat removed	0.2356	0.2301	3.8	La Motte yellow
			4.0	bromphenol blue

1. Analysis of the card teeth showed 99.6 % iron. Carbon and silicon were found present and the sulfur content was 0.071 %. Phosphorus was absent. Sulfur was determined by dissolving the iron in HCl with heat, absorbing the gas in cadmium acetate solution, precipitating with copper sulfate solution, igniting and weighing the precipitate as cupric oxide (278).

The residue in all cases was amorphous and black in color. After washing with 1:1 hydrochloric acid, it was soluble in aqua regia and disappeared on ignition. It was presumably carbon.

2. Five samples of 50 cc. each of a solution of ferrous iodide were prepared from card teeth and U.S.P. iodine, the reaction mixture being allowed to stand at room temperature until the iodine had disappeared. Apparently, little heat was retained during the course of the reaction. The solutions were heated to boiling before filtration. Analysis of only one sample was made, it showing a total iodide content of 0.23053 mols/L. and a ferrous iron content of 0.2356 mols per liter. The residue in all cases was black.

Sample	pH	Indicator
1	4.4	bromphenol blue bromcresol green
2	4.2	bromcresol green bromphenol blue La Motte yellow
3	4.1	bromphenol blue La Motte yellow
4	4.1	bromphenol blue La Motte yellow
5	4.1	bromphenol blue La Motte yellow

3. Three samples of 100 cc. each of a solution of ferrous iodide were prepared according to the U.S.P. process for Syrup of Ferrous Iodide, card teeth and U.S.P. iodine

being used in one case and Reagent iodine in the others. The reaction mixtures were heated on the water bath during the course of the reaction, care being taken to prevent loss of iodine. The residues were black. No analyses were made. The pH values of all solutions were 4.1 to La Motte yellow and bromphenol blue.

4. The pH values of solutions of ferrous iodide prepared as shown in Table 10 (p. 94), were determined colorimetrically. La Motte yellow, bromphenol blue and bromcresol green were used as indicators. No heat was used at any stage of the reaction. Sample 1 contained 0.2322 mols per liter of ferrous iron and 0.22740 mols per liter of iodide.

Sample	pH	Sample	pH	Sample	pH
1	4.4	4	4.2	6	4.1
2	4.3	5	4.1	7	4.2
3	4.1				

5. Two samples of 100 cc. each of solutions of ferrous iodide were prepared from card teeth and U.S.P. iodine, the total quantity of water to be contained in the finished preparation being used as the reaction solvent. After three days standing at room temperature, one sample was filtered and the other heated to boiling and filtered. In the former case, the pH could not be determined due to

the presence of free iodine; in the latter, analysis showed 0.23020 mols per liter of iodide and 0.2359 mols per liter of ferrous iron; the pH was 3.0 to La Motte yellow and 3.1 to bromphenol blue. Residues were black.

6. Two samples of solution of ferrous iodide of 50 cc. each, were prepared from card teeth and U.S.P. iodine. One sample was prepared corresponding to the strength specified for Syrup of Ferrous Iodide, while the other contained approximately three times this iodide content. The reaction was carried out in both cases in the refrigerator at about 4° C., chilled water being used in the reaction mixture. At the expiration of the reaction, they were heated to boiling and filtered. Residues were black in both cases.

Sample	pH	Indicator
0.23192 molar	4.1	La Motte yellow bromphenol blue
0.67110 molar	2.4	thymol blue m-cresol purple

7. In order to evaluate suggestions made in the literature that the card teeth used should be washed with alkali and acid, 5 Gm. of card teeth were placed in a boiling 10 % solution of sodium hydroxide for 10 minutes and subsequently washed thoroughly with weakly acidulated water and then with distilled water. During the treatment with alkali, the liquid acquired a brown color and some

froth containing black particles was formed. About 2 Gm. of the moist card teeth were used for the preparation of 100 cc. of solution by the reaction method of the U.S.P. X, the residue being black in color and the pH 4.1 to bromphenol blue. The above data are summarized in Table 11.

Table 11.

Effect of Variations in Manufacture upon Card Teeth Samples.

No.	Form I_2	Reaction temperature	Final temp. CO_2	Cc. made	Fe^{++} mols/ L.	Iodide mols/ L.	pH
1	USP	80°-100° C.	100°	2000	.2315	.22564	3.2
2	USP	50°- 75° C.	100°	2000	.2294	.22481	3.2
3	USP	50°- 75° C.	100°	2000	.2356	.23011	3.2
4	USP	20°- 35° C.	100°	50	.2356	.23053	4.4
5	USP	20°- 35° C.	100°	50			4.2
6	USP	25°- 35° C.	100°	50			4.1
7	USP	20°- 35° C.	100°	50			4.1
8	USP	20°- 35° C.	100°	50			4.1
9	USP	80°-100° C.	100°	100			4.1
10	Reag.	80°-100° C.	100°	100			4.1
11	Reag.	80°-100° C.	100°	100			4.1
12	USP	22° C.	22°	100	.2322	.22740	4.4
13	USP	21° C.	21°	100			4.3
14	USP	26° C.	26°	100			4.1
15	USP	23° C.	23°	100			4.2

Table 11 - cont.

Effect of Variations in Manufacture upon Card Teeth Samples.

No.	Form I_2	Reaction temperature	Final temp C°.	Cc. made	Fe^{++} mols/ L.	Iodide mols/ L.	pH
16	USP	22° C.	22°	100			4.1
17	CP	23° C.	23°	100			4.1
18	Reag.	24° C.	24°	100			4.2
19	USP	20°- 35° C.	100°	100	.2359	.23020	3.0
20	USP	4° C.	100°	50			4.1

It was concluded from the foregoing data that: (a) a molar excess of iron over iodine is contained in the finished solutions, the excess being about 0.005 mols/L.; (b) dilution of the reaction mixture deters the progress of the reaction; (c) previous washing of the card teeth with alkali and acid is without effect; (d) the pH values of the resulting solutions vary between the limits pH 3.0 and pH 4.4 according to the form of iron used; and (e) the quality of the iodine used has no effect upon the pH of the finished preparation.

In order to ascertain the effect of card teeth from various sources upon the pH values of the solutions, samples of this form of iron were obtained from several manufacturers and made up into solutions corresponding in strength to the official Syrup of Ferrous Iodide. U.S.P. iodine and

distilled water were used throughout and the reaction was carried out according to the U.S.P. directions. Results of this work, together with those obtained using C.P. and Reagent grade iodine are found in Table 12.

Table 12.

Effect of Various Samples of Card Teeth.

Source of card teeth.	Quality of I_2	pH	Iodide Gm./L.	Free Iodine
Unknown	U.S.P.	4.2	69.07	Absent
S.B. Penick	U.S.P.	4.2	70.49	Absent
Hillier's Sons	U.S.P.	4.3	71.11	Absent
Mallinckrodt	U.S.P.	4.2	70.58	Absent
Mallinckrodt	Reagent	4.2	69.32	Absent
Mallinckrodt	C.P.	4.2	70.03	Absent

As indicated in Table 12, neither variations in the card teeth nor in the quality of the iodine used had any effect upon the hydrogen ion concentration of the resulting solution.

The solution originally prepared from card teeth as obtained from Hillier's Sons Corporation precipitated almost immediately after filtration. Numerous other similar solutions were made with these card teeth but the result could not be duplicated, the solutions having a pH range of 4.1 to 4.4 and in no case precipitating upon dilution to

volume.

B. Reagent iron wire samples[1].

1. Two solutions of ferrous iodide of 2 liters each were prepared from Reagent iron and U.S.P. iodine according to the U.S.P. specifications for the reaction mixture. Analysis showed one solution to be 0.22790 molar in total iodide and 0.2349 molar with respect to iron; the other was 0.23410 molar in iodide and 0.2404 molar in ferrous iron. The residues on the filter were light brown in color. The pH of the solutions was 4.1 to bromcresol green and bromphenol blue. Precipitation occurred in the samples on diluting the filtered reaction mixtures to volume. The precipitate first appeared as colloidal matter which rapidly agglomerated, changing during the process from white to reddish-yellow.

2. Fifty cc. of solution of ferrous iodide was prepared using U.S.P. iodine but no heat was used at any point in the process. It was 0.20087 molar with respect to ferrous iodide. The residue was light brown and the pH, 4.6 to bromcresol green and 4.8 to methyl red.

The pH values for samples 8-10 as shown in Table 10

1. Reagent iron wire purchased from Merck & Co. was used throughout. Although labeled 99.8 % pure, analysis showed 99.89 % iron. Silicon was present but carbon and phosphorus were absent. The sulfur content as determined by the cadmium acetate absorption method (See foot-note p 96) was .05 %

(p 94), were as follows:

Sample	pH
8	4.6
9	4.2
10	4.4

A solution similar to those described, was boiled before filtration. It was 0.22662 molar in ferrous iodide, the residue was light brown in color and the pH was 4.2 to bromcresol green and 4.1 to bromphenol blue. All of these solutions precipitated upon diluting the reaction mixture to volume.

3. Two 50 cc. samples of solution of ferrous iodide were prepared using Reagent iodine. Heat was supplied in both cases to the reaction mixture by intermittent heating, care being taken to prevent loss of iodine. Residues were light brown in color and analysis showed 0.23000 mols per liter of ferrous iodide in one case and 0.22583 mols per liter of ferrous iodide in the other. The pH of the former was 3.4 to La Motte yellow and bromphenol blue; the latter was pH 4.1 to the same indicators. Precipitation occurred upon diluting the reaction mixture to volume.

4. Fifty cc. of a solution of ferrous iodide, prepared with Reagent iodine at about 4° C. in the refrigerator, and filtered without previous heating showed 0.2325 mols per

liter of ferrous iron and 0.23042 mols per liter of iodide. The residue was light brown and the pH was 4.2 to La Motte yellow and bromphenol blue. The solution precipitated upon diluting the reaction mixture to volume.

The above data are summarized in Table 13.

Table 13.

Effect of Variations in Manufacture on Reagent Iron Samples.

No.	Iodine used.	Reaction temp.	Final temp.	Quantity of product.	pH
1	USP	80°-100° C.	100° C.	2000 cc.	4.1
2	USP	50°- 75° C.	100° C.	2000 cc.	4.1
3	USP	20°- 35° C.	20°-35° C.	50 cc.	4.7
4	USP	22° C.	22° C.	100 cc.	4.6
5	CP	23° C.	23° C.	100 cc.	4.2
6	Reagent	22° C.	22° C.	100 cc.	4.4
7	USP	20°- 35° C.	100° C.	50 cc.	4.2
8	Reagent	80° C.	100° C.	50 cc.	3.4
9	Reagent	80° C.	100° C.	50 cc.	4.1
10	Reagent	4° C.	4° C.	50 cc.	4.2

It was concluded from these data that the quality of the iodine used, and the quantity of the solution prepared have no effect upon the pH values of the finished solutions. The volume effect observed in the preparation of samples from card teeth is not shown by Reagent iron samples and

residues differ in appearance, those from Reagent iron samples showing the characteristic green color which is obtained when ferric hydroxide is treated with potassium ferrocyanide T.S. containing a few drops of acetic acid. It was also concluded that in solutions of ferrous iodide of 2 liters or more, the pH varies from pH 3.2 for card teeth solutions to pH 4.1 for Reagent iron samples.

In order to determine the relative amounts of oxidation occurring during the progress of the reaction in samples from both sources, 100 cc. of a solution was prepared from each form of iron and Reagent iodine. The reaction was carried out in identical Erlenmeyer flasks and other conditions were made as nearly uniform as possible. At the expiration of the reactions, both solutions were heated to boiling, filtered and the residues repeatedly washed first with warm 1:1 hydrochloric acid and finally with a little distilled water. The acid filtrates were collected together with the first 3 portions of distilled wash water used, diluted to 100 cc., 5 Gm. of KI added to each and the mixture placed in an oven at 40° C. for ½ hour. From the iodine liberated as determined with 0.01 N thiosulfate solution, the following results were obtained (279):

Form of iron	Wt. of iron.	Wt. of iodine	Fe^{+++}	Wt. carbon added.
Card teeth	2.0073	6.0039	0.0089	0.00
Reagent iron	2.0151	5.9997	0.0170	0.00
Reagent iron	2.0065	6.0007	0.0100	0.50

It was concluded that the carbon present in card teeth exerts a reducing action during the progress of the reaction.

In order to determine whether or not atmospheric oxygen was the cause of this oxidation, 100 cc. of solutions of ferrous iodide were prepared from both Reagent iron and card teeth using Reagent iodine. The reaction was carried out in flasks fitted with 2 hole rubber stoppers, hydrogen being generated from zinc and sulfuric acid and passed successively through water, alkaline pyrogallol solution and the reaction mixture. After expiration of the reaction, filtration was conducted in an atmosphere of hydrogen. The residue in the case of the Reagent iron sample was negligible, appearing only as a white turbidity in the reaction mixture; in the case of card teeth, the residue was black. Upon exposure to air, the residue from the former changed slowly to reddish-brown. A solution was next prepared from card teeth and Reagent iodine, the reaction mixture being allowed to stand at room temperature for 1 week after expiration of the reaction. The residue was a mixture of black and brown material. The pH of all

solutions was 4.1. It was concluded that in the preparation of solutions of ferrous iodide from card teeth or Reagent iron, the carbon present in the former tends to minimize atmospheric oxidation which occurs in solutions prepared from the latter.

In an attempt to determine the cause of the lower pH values obtained when card teeth are used in place of Reagent iron, the two more pronounced impurities, i.e., ferrous sulfide and carbon, present in card teeth but not in Reagent iron were added to reaction mixtures of the latter. It was also reasoned that if carbon exerted an appreciable reducing action, carbon dioxide might be evolved as one of the products. Thus all reaction mixtures containing added carbon were connected with test tubes containing calcium hydroxide solution. Carbon was added as "Norite", ferrous sulfide was finely powdered and Reagent iodine was used in all cases. Reaction mixtures were heated intermittently on a water bath and finally boiled. Data follow:

Table 14.

The Effect of Impurities on pH Values.

No.	Quantity	Iron used	Carbon added	FeS	pH	CO_2
1	100 cc.	Reagent	0.1 Gm.		3.5	none
2	100 cc.	Reagent	0.2 Gm.		3.8	none
3	100 cc.	Reagent	0.3 Gm.		3.4	none

Table 14 - cont.

The Effect of Impurities on pH Values.

No.	Quantity	Iron used	Carbon added	FeS	pH	CO_2
4	100 cc.	Reagent	0.5 Gm.		3.8	none
5	100 cc.	Reagent			3.9	none
6	100 cc.	Card teeth			3.8	none
7	100 cc.	Reagent		2 Gm.	4.4	none

It was concluded that although a variation in pH values occurred in these samples, no definite relationship could be drawn as to the effect of these impurities on the pH. Likewise, no carbon dioxide was detected in any instance.

Samples Prepared by Double Decomposition. A series of samples was next prepared by double decomposition between Mallinckrodt barium iodide and Merck's Reagent ferrous sulfate, and between U.S.P. mercurous iodide and Merck's Reagent ferrous sulfate. The quantities of ingredients used were calculated stoichiometrically and weighed on the analytical balance.

1. A solution of 8.55 Gm. of barium iodide in 10 cc. of distilled water and a solution of 5.65 Gm. of Merck's Reagent ferrous sulfate in 20 cc. of distilled water were filtered separately and made up to a volume of 40 cc. each with distilled water. The solutions were mixed with constant stirring, the precipitate of barium sulfate filtered

off and the filter rinsed with enough distilled water to make 88 cc. Analysis showed 4.879 grams of iodide and 0.9235 Gm. of ferrous iron per 100 cc. The pH of the sample was 4.2 to bromphenol blue.

2. A sample prepared in the same manner as the above but using a C.P. grade of ferrous sulfate which had become partially oxidized resulted in a preparation containing traces of free iodine and having a pH of 3.2 to La Motte yellow and bromphenol blue. A portion of the same sample when heated to boiling no longer showed traces of free iodine and the pH remained unchanged.

3. A sample was prepared according to the method outlined in paragraph 1 above but the precipitate was removed by the centrifuge rather than by filtration. Analysis showed 6.28 Gm. of iodide and 1.193 Gm. of ferrous iron per 100 cc. These values correspond to 0.2028 mols per liter of iodide and 0.2118 mols per liter of ferrous iron. The pH of this solution was 4.6.

4. A solution prepared from 6.5508 Gm. of U.S.P. yellow mercurous iodide and 2.7802 Gm. of Merck's Reagent ferrous sulfate by adding a solution of the latter to a suspension of the former in 25 cc. of water and subsequent centrifuging and dilution to 100 cc., showed an iodide

content of 4.202 Gm. of ferrous iodide per 100 cc. The pH of the solution was 4.7 to bromcresol green.

It was concluded from these data that ferrous iodide solutions prepared by double decomposition, tend to assume higher pH values except in the case where impurities are present, than do solutions made by the direct union reaction.

The Ferrous Iron Content of Solutions of Ferrous Iodide. Since ferrous iodide might be expected to hydrolyze in aqueous solutions, a supposition supported by the hydrogen ion concentrations previously determined, it would appear probable from the known characteristics of the compounds concerned that the hydrolysis might be represented by the two following equations:

(I) $FeI_2 + HOH \rightleftharpoons Fe(OH)I + HI$

(II) $FeI_2 + 2\ HOH \rightleftharpoons Fe(OH)_2 + 2\ HI.$

In the reaction mixture, however, an excess of iron is present and some possibility exists that the hydriodic acid formed during hydrolysis would react with iron, thus causing the finished solution to contain an excess of iron as compared to the calculated quantity of iodine. Some indication of such reaction has already been given by the results (Table 11) which show that card teeth solutions contain a molar excess of iron. In order to determine

whether this excess iron is commonly contained in all solutions of ferrous iodide, a series of experiments was performed in which volumetric determinations were carefully checked by means of a gravimetric procedure.

Samples of solutions of ferrous iodide were prepared both with card teeth and with Reagent iron using definite weighed quantities of U.S.P. iodine and the iron in question. At the expiration of the reaction, the excess iron was separated by filtration, dissolved in warm nitric acid, precipitated with ammonium hydroxide, filtered through an ashless filter, washed and ignited and weighed as ferric oxide (280). The data obtained from three samples of such a solution as prepared from card teeth and U.S.P. iodine are contained in Table 15. The weight of iron which should have been consumed is calculated stoichiometrically from the equation:

$$Fe + I_2 \rightleftharpoons FeI_2$$

Table 15.

Relation between Iron and Iodine in Reaction Mixture.

	Gm. Iodine used.	Gm. Fe used.	Gm. Fe_2O_3 found	Gm. Fe excess	Gm. Fe reacted	Gm. Fe (calc)	Gm. Fe excess
(1)	6.0460	2.0110	.96542	.67523	1.33577	1.32994	.00583
(2)	6.0000	2.0070	.95470	.66773	1.33927	1.31982	.01945
(3)	6.0020	2.0042	.95489	.66785	1.33637	1.32029	.01608

Table 15 - cont.

Relation between Iron and Iodine in Reaction Mixture.

Excess Fe mols/L. in sol.	Iodide mols/L.	Iron mols/L. (vol)	Excess iron mols/L. Volumetric	Excess Fe mols/L. Grav.
(1) 1.04×10^{-3}	.23212	.2332	1.07×10^{-3}	1.04×10^{-3}
(2) 3.48×10^{-3}	.23431	.2343	2.91×10^{-3}	3.48×10^{-3}
(3) 2.88×10^{-3}	.23673	.2392	2.45×10^{-3}	2.88×10^{-3}

As indicated in Table 15, a greater quantity of iron is used in the reaction than can be accounted for by the calculated values. Volumetric analyses of the same solutions indicate that an excess corresponding to the excess iron used is present in the sample.

A similar series of data for solutions prepared from Reagent iron is contained in Table 16.

Table 16.

Relation between Iron and Iodine in Reaction Mixture.

Gm. Iodine used.	Gm. Fe used.	Gm. Fe_2O_3 found	Gm. Fe excess	Gm. Fe reacted	Gm. Fe (calc)	Gm. Fe excess
(1) 6.06351	2.1010	1.0303	.72061	1.38039	1.33350	.04689
(2) 6.02010	2.0057	0.9153	.64013	1.36557	1.32430	.04127
(3) 5.98720	2.0139	0.9319	.65177	1.36213	1.31690	.04523

Table 16 - cont.

Relation between Iron and Iodine in Reaction Mixture.

Excess Fe mols/L. in sol.	Iodide mols/L.	Iron mols/L. (vol)	Excess iron mols/L. Volumetric	Excess Fe mols/L. Grav.
(1) 8.40×10^{-3}	.2388	.2451	6.30×10^{-3}	8.40×10^{-3}
(2) 7.39×10^{-3}	.2372	.2452	8.03×10^{-3}	7.39×10^{-3}
(3) 8.10×10^{-3}	.2358	.2451	9.27×10^{-3}	8.10×10^{-3}

As indicated by the data in Table 16, Reagent iron samples are similar to those prepared from card teeth in that an excess of iron is used in the progress of the reaction, and this excess appears in the finished preparation. A comparison with Table 15, also shows that the excess iron contained in the Reagent iron samples is greater than in samples prepared from card teeth. This excess is probably due to the presence of additional iron as the basic salt or as dissolved ferrous hydroxide.

Unsaturated Hydrocarbons in the Reaction Mixture. It has been thought that the carbon contained as an impurity in card teeth is the cause of the formation of hydrocarbons during the progress of the reaction. In order to determine whether or not any unsaturated hydrocarbons are developed, various samples of solution of ferrous iodide were prepared in which the reaction mixture was contained in a flask whose only outlet was through standardized potassium

permanganate solution. The mixture was boiled vigorously at the end of the reaction and the permanganate titrated with a freshly prepared solution of Mohr's salt. In each case, a blank determination was run in conjunction with the actual boiling process. It was concluded from three experiments of this nature that no unsaturated hydrocarbons were volatilized by boiling the reaction mixture.

Variation of the Hydrogen Ion Concentration with Time. The pH value of all solutions described in the previous sections of this thesis were determined after 12 to 24 hours standing in the presence of air. In every case, the pH of the solution measured was 3.1 to La Motte yellow and 3.2 to bromphenol blue. Precipitation invariably accompanies increase in acidity for samples prepared from Reagent iron but does not occur until after the pH of 3.1 or 3.2 is attained for other samples. This latter pH remains constant for all samples over a period of 1 year, although continued precipitation occurs. A similar behavior has been observed for numerous salts by Denham (281).

In order to obtain data regarding this change in pH, the hydrogen ion concentration of typical solutions was measured colorimetrically at short intervals using the usual indicators and compared with similar data from

solutions of ferrous sulfate of comparable concentration.

Table 17.

Variation of pH with Time.

Solutions of Ferrous Iodide and Ferrous Sulfate.

Time	Sol.[1] FeI_2 pH	Sol.[2] FeI_2 pH	Sol.[3] FeI_2 pH	Sol.[4] $FeSO_4$ pH	Sol.[5] $FeSO_4$ pH
0	4.6	4.1	4.1	4.1	3.1
½ hour	4.4	4.1	4.1	4.1	3.1
1 hour	4.2	4.1	4.1	4.1	3.1
1½ hours	4.1	4.1	4.0	4.0	3.1
2 hours	4.1	4.0	4.0	4.0	3.1
2½ hours	4.1	4.0		4.0	3.1
3 hours	4.0	4.0	3.8	3.9	3.1
3½ hours	3.8	3.9		3.9	3.1
4 hours	3.6	3.9	3.7	3.8	3.2
4½ hours	3.5	3.9		3.7	3.2

1. A solution of ferrous iodide prepared by double decomposition between Merck's Reagent ferrous sulfate and barium iodide.
2. A solution of ferrous iodide prepared by direct union between Reagent iron and Reagent iodine in an atmosphere of hydrogen.
3. A solution of ferrous iodide prepared from card teeth and Reagent iodine.
4. A solution of ferrous sulfate prepared by solution of the recrystallized Reagent grade salt in distilled water.
5. A solution of ferrous sulfate prepared by solution of the Reagent grade salt in distilled water.

Table 17 - cont.

Variation of pH with Time.

Solutions of Ferrous Iodide and Ferrous Sulfate.

Time	Sol.[1] FeI_2 pH	Sol.[2] FeI_2 pH	Sol.[3] FeI_2 pH	Sol.[4] $FeSO_4$ pH	Sol.[5] $FeSO_4$ pH
5 hours	3.4	3.9	3.4	3.5	3.1
6 hours	3.2	3.9		3.2	3.2
8 hours		3.7			3.2
10 hours	3.2	3.4	3.2	3.2	3.2
15 hours	3.2	3.2		3.2	3.2
1 year	3.2	3.2	3.2	3.2	3.2

It was concluded that solutions of ferrous iodide, regardless of the original pH value tend to come to equilibrium at pH 3.1 to pH 3.2 at which point they remain over a period of 1 year or longer. Some evidence is also present to indicate the formation of a primary equilibrium at pH 4.1 although this is in any event only temporary. These results are in accord with those of Wintgen and Biltz who found values closely approximating these when ferric hydroxide sols are measured by means of glass electrodes (160).

4. The Hydrolysis of Ferrous Iodide.

Of the many investigators who have worked upon Syrup of Ferrous Iodide, only a few have attached any importance to

the acid reaction of the preparation. In fact, the U.S.P. VIII specified that the finished preparation should be neutral in reaction, a condition obviously incompatible with the nature of the preparation. Richard Phillips Jr., in 1845, suggested that ferrous iodide reacted with water to form hydriodic acid and ferrous oxide, the former then deteriorating to liberate free iodine, but his theory was not based upon experimental determinations and apparently found no favor with other investigators. Krantz, at a much later date, measured the pH value of the finished Syrup but attached no particular importance to the value he obtained. To the best of our knowledge, no attempt has been made to study hydrogen ion concentrations or degree of hydrolysis in Syrup of Ferrous Iodide. Consequently, such a study was undertaken in order to clarify this point.

Ferrous iodide, being the salt of a weak base, i.e., ferrous hydroxide, and a strong acid, i.e., hydriodic acid, it is logical to expect hydrolysis to occur in an aqueous solution of the salt. Since, however, neither the hydrogen nor the quinhydrone electrodes may be used to measure the concentration of hydrogen ions in the solution, and the electrolytic constant for the base concerned is not available in the literature, recourse was had to the colorimetric estimation of pH values of the solution in order to determine

the approximate degree of hydrolysis of the salt. A La Motte block color comparator and the usual La Motte color standards and indicator solutions were used and the pH values determined for ferrous iodide solutions as previously explained.

In dealing with salts of multivalent cations, the hydrolysis may occur progressively in several stages, to each of which correspond definite equilibria[1]. In the case of ferrous iodide, the progressive stages of hydrolysis may be represented by the following purely stoichiometric equations:

(I) $FeI_2 + H_2O \rightleftharpoons Fe(OH)I + HI$

(II) $FeI_2 + 2H_2O \rightleftharpoons Fe(OH)_2 + 2HI$

The mechanism of equation (I) is represented by the ionic equilibria:

(III) $(FeI)^+ + (OH)^- \rightleftharpoons Fe(OH)I$

(IV) $(H)^+ + (OH)^- \rightleftharpoons H_2O$

which may be combined in the simple equilibrium equation:

(V) $(FeI^+) + H_2O \rightleftharpoons Fe(OH)I + H^+$

Denoting molar concentrations by square brackets, and applying the Law of Mass Action to equation (III),

(VI) $K_{b_1} = \frac{[FeI][OH^-]}{[Fe(OH)I]}$

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1. Similar mathematical expressions were developed by Denham (281) for the hydrolysis of salts containing a poly-valent ion.

and similarly

$$(VII)\quad K_w = [OH^-]\ [H^+]\ ;\ [OH^-] = K_w/[H^+]$$

and therefore, substituting equation (VII) into equation (VI),

$$(VIII)\quad \frac{K_w}{K_{b_1}} = \frac{[Fe(OH)I]\ [H^+]}{[FeI]}$$

If we now make the simplifying assumptions that ferrous iodide and hydriodic acid are completely ionized according to the equations:

$$FeI_2 \rightleftharpoons FeI^+ + I^-$$

$$HI \rightleftharpoons H^+ + I^-$$

and if v denotes the molar dilution of the total ferrous iodide (hydrolyzed and non-hydrolyzed), and if z is the fractional amount hydrolyzed, it follows from the above equations and assumptions, that

$$[FeI^+] = \frac{1-z}{v}\ ;\ [H^+] = [Fe(OH)I] = z/v$$

whence from equation (VIII), we have,

$$(IX)\quad \frac{K_w}{K_{b_1}} = \frac{z/v \cdot z/v}{1 - z/v} = \frac{z^2}{v(1-z)} = K_1$$

It must be observed that z represents the fractional amount of hydrolysis according to the first stage (equation I) and since the hydrogen ion concentration of water is small compared to that resulting from the hydrolysis of ferrous iodide, it can be neglected and it may be assumed that

$$[H^+] = [Fe(OH)I] = z/v$$

This assumption is generally made in such cases. The first stage hydrolysis is due to the formation of the relatively undissociated basic salt, Fe(OH)I, which may be regarded as the hydroxide of the complex cation $(FeI)^+$.

We now consider a state of affairs wherein the hydrolysis corresponds to the stoichiometric equation (II), that is to say, to the formation of the relatively undissociated free base, $Fe(OH)_2$ which reaction we may suppose to occur in more dilute solutions. Assuming complete dissociation of ferrous iodide according to the equation

$$FeI_2 \rightleftharpoons Fe^{++} + 2\ I^-$$

and a hydrolysis controlled by the dissociation equilibrium:

$$Fe^{++} + 2\ OH^- \rightleftharpoons Fe(OH)_2$$

we have

$$(X) \qquad K_{b_2} = \frac{[Fe^{++}]\ [OH^-]^2}{[Fe(OH)_2]}$$

or since

$$(XI) \qquad [OH^-]^2 = \frac{K_w^2}{[H^+]^2}$$

then

$$(XII) \qquad \frac{K_w^2}{K_{b_2}} = \frac{[Fe(OH)_2]\ [H^+]^2}{[Fe^{++}]}$$

and therefore, since

$$[Fe^{++}] = 1-z/v\ ;\ [Fe(OH)_2] = z/v\ ;\ [H^+] = 2\ z/v$$

then

(XIII) $$\frac{K_w^2}{K_{b_2}} = \frac{z/v \cdot (2\,z/v)^2}{1 - z/v} = \frac{4\,z^2}{v^2(1-z)} = K_2$$

Thus it is evident that the hydrolysis of ferrous iodide may progress in two stages but it must be remembered that (a) the progressive stages may not be sharply defined but considerable superposition may occur, (b) the solubility of basic salts or hydroxides may be overstepped so that heterogeneous equilibria are produced, (c) the basic salt or hydroxide may separate in the form of colloidal pseudo-solutions or suspensions thus giving no definite equilibria, (d) the above derivation is in terms of concentration rather than activity, and (e) certain assumptions have been made which do not hold in the strictest sense.

Upon considering the data in Table 17 as well as the pH values of solutions prepared in this work, it would appear probable that two distinct hydrolytic equilibria are to be considered, i.e., a temporary equilibrium at about pH 4.1 and a permanent equilibrium at about 3.2

From a consideration of the theory involved it is apparent that the predominant type of hydrolysis as well as the degree of hydrolysis may be determined approximately from the hydrogen ion concentrations of the solution, constant values of the hydrolytic constant K_1 or K_2 being satisfactory proof of the stage of hydrolysis

occurring. In this connection, it is well to note that a steadily decreasing series of values for K_2, upon dilution, will indicate basic salt formation (282). In order to determine the type and degree of hydrolysis, a solution of ferrous iodide was prepared from Reagent iron and Reagent iodine in an atmosphere of hydrogen and analyzed. One half of this solution was subjected to a series of dilutions and the pH values obtained; the other half was allowed to reach a pH of 3.1 to 3.2 and similarly tested over a range of dilutions. The data obtained together with the calculated hydrolysis constants and degrees of hydrolysis follow in Tables 18 and 19. The values of K_1 were calculated from equation (IX), assuming z to be equivalent to $v[H^+]$ and the values of K_2 were calculated from equation (XIII), assuming z to be equivalent to $v[H^+]/2$. The column 100 z refers to the degree of hydrolysis on the basis

$$z = v[H^+]$$

since equation (IX) was found to be applicable.

Table 18.

Degree of Hydrolysis of Ferrous Iodide Solutions.

Primary Equilibrium.

Conc. mols/L.	v	pH	$[H^+]$	100 z	$K_1 \times 10^7$	$K_2 \times 10^7$
0.2350	4.255	4.20	6.31×10^{-5}	0.027	0.17	0.53
0.1175	8.511	4.35	4.47×10^{-5}	0.038	0.17	0.38
0.05875	17.022	4.70	2.00×10^{-5}	0.034	0.07	0.07
0.029375	34.044	4.95	1.12×10^{-5}	0.038	0.04	0.02
0.014688	68.088	5.05	8.91×10^{-6}	0.061	0.05	0.02
0.007344	136.176	5.15	7.08×10^{-6}	0.096	0.07	0.02
0.003672	272.352	5.20	6.31×10^{-6}	0.172	0.11	0.03

From these data it was concluded that a primary equilibrium exists in solutions of ferrous iodide of concentration comparable to the strength of the U.S.P. Syrup at pH 4.1 to 4.2. The equilibrium in this case may be represented by the equation:

$$FeI_2 + H_2O \rightleftharpoons Fe(OH)I + HI$$

and the degree of hydrolysis is approximately 0.027 % at the concentration of the official Syrup of Ferrous Iodide.

Table 19.

Degree of Hydrolysis of Ferrous Iodide Solutions.

Secondary Equilibrium.

Conc. mole/L.	v	pH	$[H^+]$	100 s	$K_1 \times 10^8$	$K_2 \times 10^{11}$
0.2360	4.238	3.15	7.08×10^{-4}	.30	2.12	75.23
0.1180	8.476	3.55	2.82×10^{-4}	.24	.67	9.49
0.0590	16.952	3.80	1.59×10^{-4}	.27	.43	3.38
0.0295	33.904	4.05	8.91×10^{-5}	.30	.26	1.20
0.01475	67.808	4.30	5.02×10^{-5}	.34	.17	.43
0.00738	135.616	4.40	3.98×10^{-5}	.54	.21	.42
0.00369	271.232	4.60	2.51×10^{-5}	.68	.17	.21

Although the values of the equilibrium constant K_1 are not in as good agreement in Table 19 as in Table 18, they are sufficiently good when taken in conjunction with the rapidly decreasing values of K_2 down to a dilution of 33 liters, to allow us to conclude that the same reaction is predominant at secondary equilibrium as occurs at primary equilibrium. In this case, the degree of hydrolysis at the concentration corresponding to the U.S.P. syrup is approximately 0.30 %.

In order to determine the effect of the addition of other substances commonly used as preservatives, upon the hydrolysis of ferrous iodide, solutions were prepared containing sucrose, dextrose, lactose, honey, glycerin and

alcohol and the pH values noted colorimetrically. Whenever solubility would allow, 2.484 mols of preservative were used per liter of solution, this value corresponding to the strength of the U.S.P. syrup with respect to sucrose. The molecular weight of honey being indeterminate, however, a quantity corresponding approximately to the calculated weight of dextrose was used. Data follow in Table 20.

Table 20.

pH Values of Ferrous Iodide Syrups.

Form of Iron	Sugar or Other ingredient.	Quantity of preservative	pH	Indicator
Card teeth	sucrose	2.484 mols/L.	2.6	m-cresol purple.
Card teeth	dextrose	2.484 mols/L.	2.5	thymol blue.
Reagent iron	sucrose	2.484 mols/L.	4.2	bromocresol green.
Card teeth	lactose	.470 mols/L.	2.7	La Motte yellow.
Card teeth	honey	500 Gm. per L.	2.6	m-cresol purple.
Card teeth	glycerin	2.484 mols/L.	3.9	bromphenol blue.
			3.5	La Motte yellow.
Card teeth	alcohol	2.484 mols/L.	3.2	La Motte yellow.

As indicated in Table 20, the pH value of a syrup

prepared from Reagent iron corresponds with that of a solution similarly prepared. On the other hand, a syrup prepared from card teeth shows a lower pH than a similar solution. This observation also applies to syrups prepared with dextrose, honey and lactose, but alcohol has no apparent effect upon the pH. A glycerin containing solution gives widely variant results with two indicators, this variation probably being due to the effect of glycerin upon the dissociation constants of the indicators.

The apparent anomaly concerning the hydrogen ion concentrations observed in syrups prepared with Reagent iron and card teeth can be explained within the limits of experimental error by a consideration of the volume of the syrup occupied by the sugar, the degree of hydration of the sugar and the hydrolysis constants corresponding to the respective equilibria. Due to the volume occupied by the sucrose, only 490 cc. of water were used in each of these syrups per liter of finished product. This represents a total of 27.22 mols of water per liter of syrup. Assuming that sucrose forms a hexahydrate (283), 2.484 mols of sucrose would combine with 14.904 mols of water thus leaving only 12.32 mols of "solvent" water in the syrup. We may consider, therefore, that the molarity is increased with reference to ferrous iodide and we have 0.236 mols of the salt dissolved in 12.32 mols of water or an actual

molarity of 1.062 with respect to ferrous iodide.

Considering first the Reagent iron syrup and using the mean of the values obtained at primary equilibrium for the hydrolysis constant in Table 18, i.e., approximately 1.0 x 10^{-8},

$$K_h = \frac{z^2}{v\,(1-z)} = \frac{v^2[H^+]^2}{v\,(1-z)} = v\,H^2$$

where (1-z) is regarded as being unity. Thus in this case

$$1 \times 10^{-8} = \frac{[H^+]^2}{1.062}$$

and

$$[H^+] = 1.02 \times 10^{-4}$$

or

$$pH \backsim 4.0$$

Treating the card teeth solution similarly but using the secondary equilibrium value[1] obtained from Table 19,

$$K_h^* = 2.12 \times 10^{-6}$$

then

$$2.12 \times 10^{-6} = \frac{[H^+]^2}{1.062}$$

or

$$[H^+] = 1.50 \times 10^{-3}$$

and

$$pH = 2.8$$

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1. It will be remembered that large volumes of card teeth solutions tend to attain secondary equilibrium before filtration.

*. This value is chosen, rather than the mean, as being more nearly representative of concentrated solutions.

Thus, from these results, it is evident that due to the difference in the value of the hydrolysis constant in the two cases, changes in concentration do not greatly affect the pH values of solutions prepared from Reagent iron but do cause marked decreases in the pH values of solutions prepared from card teeth at secondary equilibrium. It was concluded that the increased concentration of ferrous iodide, due to the volume occupied by the sucrose and its state of hydration, may be responsible for the variations in pH obtained in Syrup of Ferrous Iodide prepared from different forms of iron.

5. The Decomposition of Ferrous Iodide.

Conditions of Precipitation. If we consider a solution of ferrous iodide 0.236 molar in strength[1], the usual acidity of the solution has been shown to be approximately pH 4.0. On the other hand, since the reaction itself is carried out in 1/5 of the volume of the finished product, the reaction mixture is actually 5 x 0.236 or 1.18 molar with respect to ferrous iodide. Using the mean of the primary equilibrium values of K_h as determined in Table 18, i.e., approximately 1×10^{-8}, and since

$$(I) \quad K_h = \frac{z^2}{v(1-z)} = \frac{[H^+]^2 v^2}{v(1-z)} = \frac{v[H^+]^2}{(1-z)}$$

1. This value is chosen as representing the approximate strength of the U.S.P. Syrup of Ferrous Iodide.

or if z is small, (1-z) becomes nearly unity and

$$(II) \qquad K_h = v[H^+]^2$$

or

$$1 \times 10^{-8} = v[H^+]^2$$

and substituting the value 1/1.18 for v and solving for $[H^+]$, we obtain

$$[H^+] = 1.09 \times 10^{-4}$$

Since

$$(III) \quad K_w = [OH^-][H^+] = 1 \times 10^{-14}$$

then

$$[OH^-] = 1 \times 10^{-14} / 1.09 \times 10^{-4} = 9.16 \times 10^{-11}$$

Thus the $[OH^-]$ concentration of the preparation should be approximately 9.16×10^{-11} in the reaction mixture.

Since:

$$(IV) \qquad K_s = [Fe^{+++}][OH^-]^3$$

then

$$(V) \qquad [Fe^{+++}] = K_s / [OH^-]^3$$

On substituting the values obtained for the reaction mixture, we have

$$[Fe^{+++}] = \frac{1.1 \times 10^{-36}}{(9.16 \times 10^{-11})^3} = 1.43 \times 10^{-6}$$

Since each mol of ferrous iron furnishes upon oxidation, one mol of ferric iron, and the solution is 1.18 molar, it is evident that

$$1.43 \times 10^{-6} \times 100 / 1.18 = 1.21 \times 10^{-4} \%$$

or slightly more than 1/10,000 % of ferrous iron need be oxidized to cause precipitation.

Similarly in the finished solution, at pH 4.0 or pOH 10.0, the $[OH^-]$ will be equal to 1×10^{-10}, and

$$[Fe^{+++}] = \frac{1.1 \times 10^{-36}}{(1 \times 10^{-10})^3} = 1.1 \times 10^{-6}$$

or

$$0.0000011 \times 100 / 0.236 = 0.00046 \%$$

and therefore it would be necessary for 0.00046 % of the total ferrous ion present to be converted to the ferric state for precipitation to occur. If we now consider the finished Syrup of Ferrous Iodide in the same light, the solubility of ferric hydroxide in 50 % sucrose solutions has been given as 2.18×10^{-5} mols per liter or the solubility product is:

$$K_s = (0.0000218)(0.0000654)^3 = 6.08 \times 10^{-18}$$

Thus if we assume the maximum alkalinity of the syrup which has been shown to be about pH 5.0 and complete oxidation of the ferrous salt, the ion product will be:

$$K = 0.236 \times (1 \times 10^{-9})^3 = 2.36 \times 10^{-26}$$

and it is evident that ferric hydroxide cannot precipitate in the official preparation.

If we now consider a solution of ferrous iodide prepared from card teeth and showing a pH of approximately

3.0, the pOH will be 11.0 and the $[OH^-]$ will be 1×10^{-11}, thus

$$[Fe^{+++}] = \frac{1.1 \times 10^{-36}}{(1 \times 10^{-11})^3} = 0.0011$$

and

$$0.0011 \times 100 / 0.236 = 0.46\ \%$$

or nearly ½ of 1 % of the ferrous ion present must be oxidized to cause precipitation. If we consider the reaction mixture in this case in the same light, and assume the value[1] 2.12×10^{-6} as the hydrolysis constant from Table 19, and apply equations (I) to (V), we obtain

$$[Fe^{+++}] = K_h / (OH^-)^3 = \frac{1.1 \times 10^{-36}}{(8.13 \times 10^{-22})^3} = 2.4 \times 10^{-3}$$

and

$$2.4 \times 10^{-3} \times 100 / 1.18 = 0.223\ \%$$

Thus in the card teeth reaction mixture which furnishes a solution of pH 3.0, 0.223 % of the total ferrous ion must be oxidized to cause precipitation of ferric hydroxide.

The above data are summarized in Table 21:

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1. In this case, the value 2.12×10^{-6} was chosen for K_h rather than the mean of the determinations in Table 19 since it more nearly represents the conditions in more concentrated solutions.

Table 21.

Precipitation of Ferric Hydroxide.

Type of solution	Place	% oxidation for ppt.	mols Fe^{+++} for ppt.
Reagent iron pH 4.1	reaction mixture	1.21×10^{-4}	0.00000143
	finished solution	4.6×10^{-4}	0.0000011
Card teeth pH 3.1	reaction mixture	0.223	0.0024
	finished solution	0.46	0.0011
U.S.P. Syrup		no ppt.	

Thus it is evident that precipitation occurs most readily in the reaction mixture of solutions of about pH 4.1 and with the greatest difficulty in card teeth solutions of about pH 3.1.

If we consider next the solubility of air in water at 20° C., the approximate temperature at which dilution of the reaction mixture is made, and assume the water used to be saturated with air, 1000 cc. of water contain 18.68 cc. of air of which 34.03 % is oxygen (284). Reducing this value to 0° C. and stating it in terms of mols per liter, we have

$$\frac{18.68 \times 0.3403 \times 273 \times 32}{293 \times 22,400 \times 32} = 0.000264 \text{ mols/L.}$$

Upon the basis:

$$2\ Fe(OH)_2 + H_2O + \tfrac{1}{2}\ O_2 \rightleftharpoons 2\ Fe(OH)_3$$

one mol of oxygen will convert four mols of ferrous iron to the ferric condition. Thus the total oxygen in one liter of a solution of ferrous iodide would be sufficient to convert

$$4 \times 0.000264 = 0.001056 \text{ mols/L.}$$

of ferrous to ferric iron. Upon comparing this value with the data shown in column 4, Table 21, it is evident that insufficient oxygen is present to cause precipitation in solutions of card teeth at secondary equilibrium, but that immediate precipitation should be expected to occur in solutions prepared from Reagent iron. This explanation is in accordance with observed experimental data.

If we next consider ferrous hydroxide in the same manner and accept the solubility product as (p 49)

$$K_s = 1.6 \times 10^{-14}$$

and use the values calculated above for the hydroxyl ion concentrations of both reaction mixtures and finished solutions, we have as the precipitation points for a reaction mixture containing Reagent iron,

$[Fe^{++}] = 1.6 \times 10^{-14} / (9.16 \times 10^{-11})^2 = 1.91 \times 10^{6}$ mols/L.

and for a finished solution from Reagent iron,

$[Fe^{++}] = 1.6 \times 10^{-14} / (1 \times 10^{-10})^2 = 1.6 \times 10^{6}$ mols/L.

and it is evident that since the solution is 1.18 molar in

the former and 0.236 molar in the latter case with respect to ferrous ion, no precipitation will occur. Likewise, since the precipitation points increase with a decrease in the hydroxyl ion concentration, no precipitation should occur in samples from card teeth or at secondary equilibrium in either solution. It would also be expected that no precipitation should occur in the syrup.

The Mechanism of Iodine Formation. The decomposition of solutions containing ferrous iodide alone consists entirely in the formation of free iodine and ferric hydroxide; in syrups prepared without a preservative, however, ferric hydroxide does not precipitate but a permanent dark coloration, other than that due to iodine, appears on long standing. The presence of ferric ion in solution is of course prohibited by the presence of iodide ion which reacts with it to form ferrous iron and free iodine.

In any case, the appearance of free iodine may be regarded as due to thermal or photochemical oxidation of iodide ion, to spontaneous decomposition of the type

$$2\,HI \rightleftharpoons H_2 + I_2$$

to stoichiometric molecular oxidation of ferrous iodide, or to spontaneous decomposition of ferrous iodide molecules according to the equation:

$$FeI_2 \rightleftharpoons Fe + I_2$$

Of these several types of decomposition, the last named is not acceptable either on theoretical grounds or upon an experimental basis, since no metallic iron has been found in deteriorated solutions of ferrous iodide.

Reference to the theories of decomposition advanced by other investigators (p 75-81) shows that relatively few equations have been advanced to account for this phase of decomposition. Salzer (235) and Sadtler and Coblentz (268) formulated the equation

(I) $FeI_2 + 2\ HOH + \frac{1}{2}\ O_2 \rightleftharpoons Fe(OH)_3 + HI + I$

Mylius (253) suggested

(II) $2\ FeI_2 + 3\ O_2 + 3\ HOH \rightleftharpoons 2\ Fe(OH)_3 + I_2$

and Bentley and Driver (264) account for the decomposition by a series of two reactions:

(III) $2\ FeI_2 + O_2 \rightleftharpoons 2FeOI + I_2$

(IV) $FeOI + 2\ HOH \rightleftharpoons Fe(OH)_3 + HI$

Phillips (248) believed the decomposition to be due to oxidation of the hydriodic acid formed by hydrolysis but did not verify his assumption.

Considering the above equations from a stoichiometric standpoint, it is evident that all three equations require the loss of two mols of ferrous iron per mol of free iodine

liberated. Equation (I), however, shows that due to the formation of hydriodic acid which would subsequently deteriorate, the partially decomposed solution should contain somewhat more than 1 mol but not more than 2 mols of iodine for each two mols of ferrous iron loss. Equation (IV) also would require the presence, in a partially decomposed solution, of more than the stoichiometric quantity of iodine since HI is formed.

In order to determine the validity of the equations given and to obtain further data relative to the mechanism of the decomposition, experiments were carried out so designed as to compare the loss of ferrous iron with the increase in free iodine content in aqueous solutions of ferrous iodide. Samples of aqueous solutions of ferrous iodide prepared either from card teeth or C.P. iron wire were prepared in the usual fashion, assayed and stored at 30° C. in the thermostat either in half filled, 2 liter acid bottles, in completely filled one ounce prescription bottles, or in completely filled, sealed pycnometers and the ferrous iron and iodine content determined quantitatively at various intervals. Ferrous iron was determined by the method outlined earlier in this thesis and iodine was determined with approximately 0.01 N sodium thiosulfate solution using starch T.S. as the indicator.

Table 22, following, shows the data as obtained from an aqueous solution of ferrous iodide prepared from card teeth and U.S.P. iodine and stored under the conditions described above in a half filled acid bottle. The solution assayed 0.2256 mols per liter of total iodide by the U.S.P. method, or well within the limits of strength as prescribed for Syrup of Ferrous Iodide. Precipitation occurred in the solution in approximately 12 hours although iodine was apparent in 20 minutes. For convenience in comparison of data, column 4 shows the ratio between loss of molarity of ferrous iron and molarity in iodine. Thus, if the reaction takes place as supposed in equations I, II and III above, this ratio should be about 2 : 1.

Table 22.

Ratio of Molarity of Iron and Iodine in Card Teeth Solutions

Hours	Loss Fe^{++} mols/L.	I_2 mols/L.	Fe^{++}/I_2
0	-----	-------	-----
172.5	0.00772	0.00144	5.36
240	0.00799	0.00177	4.52
292	0.00705	0.00197	3.58
340	0.00705	0.00220	3.20
384	0.00705	0.00313	2.26
436	0.01089	0.00337	3.21
557	0.01614	0.00418	3.86

Table 22.- cont.

Ratio of Molarity of Iron and Iodine in Card Teeth Solutions

Hours	Loss Fe^{++} mols/L.	I_2 mols/L.	Fe^{++} / I_2
774	0.02094	0.00561	3.72
918	0.02093	0.00666	3.14
1178	0.01983	0.00897	2.21
1538	0.03675	0.01300	2.82
		Average--	3.44

As indicated by the data in Table 22, the ratios of ferrous iron loss per mol of iodine are invariably greater than the limiting ratio of 2 : 1 required for the validity of the equations previously mentioned.

It was concluded that there was no relationship between the decrease in ferrous iron and the free iodine formed in ferrous iodide solutions.

A sample of aqueous ferrous iodide assaying 0.2273 mols per liter of total iodide by the U.S.P. method was next prepared, using in this case, however, C.P. iron wire and U.S.P. iodine. The experimental procedure was similar to that given above and the data are shown in Table 23.

Table 23.

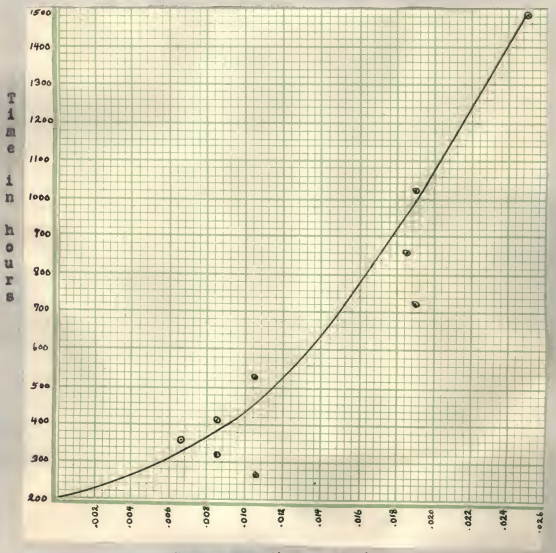
Molarity Ratio of Iron and Iodine in Reagent Iron Solutions.

Hours	Loss Fe^{++} mols/L.	I_2 mols/L.	Fe^{++}/I_2
0	------	-----	-----
215	------	0.00143	-----
263	0.0104	0.00163	6.39
315.5	0.0085	0.00167	5.07
359	0.0066	0.00231	2.85
411	0.0085	0.00272	3.13
532	0.0104	0.00341	3.05
719	0.0189	0.00446	4.24
863	0.0183	0.00503	3.63
1123	0.0193	0.00639	3.02
1483	0.0254	0.00789	3.22

The analyses for iron in the above tables are, in certain instances, not in good agreement. These discrepancies are due, in all probability, to the magnification of titration errors occurring in the calculation of data on such dilute solutions. The following graph, however, plotted from the data in Table 23, indicates that the agreement is rather better than appears from an inspection of column 2.

Fig. 1

Graph showing the Loss of Ferrous Iron by Auto-Oxidation in Aqueous Solutions of Ferrous Iodide prepared from Reagent Iron and Reagent Iodine. Data plotted from Table 23, column 2 (Page 140).



Loss of Fe^{++} in mols/L.

A liter of solution of ferrous iodide in water was next prepared from card teeth and iodine and placed in dry one ounce prescription bottles. These bottles were almost completely filled, the stopper coated with wax and pressed tightly into the bottle, tied securely with cord and the whole neck immersed in melted paraffin. These bottles, which contained only very small amounts of air, were placed in the thermostat at 30° C. Due to the fact that each bottle contained slightly different amounts of air, each value below must be taken as a separate experimental fact, i.e., there is no vertical relationship between the data. The conditions of this experiment amount to a nearly complete cessation of the decomposition at the expiration of the contained air. Data follow in Table 24.

Table 24.

Molarity Ratio of Iron and Iodine in Absence of Excess Air.

Hours	Loss Fe^{++} mols/L.	I_2 mols/L.	Fe^{++}/I_2
0	-----	-----	-----
90	-----	0.000310	-----
214	0.00109	0.000272	4.01
266	-----	0.000285	-----
310	-----	0.000125	-----
358	0.01480	0.000435	3.41
410	0.00241	0.000476	5.07

Table 24 - cont.

Molarity Ratio of Iron and Iodine in Absence of Excess Air.

Hours	Loss Fe^{++} mols/L.	I_2 mols/L.	Fe^{++}/I_2
531	0.00387	0.000448	8.64
603	0.00423	0.000190	2.21
718	0.00123	0.000271	4.52
866	0.00461	0.000951	4.83

From the above data, it was again concluded that no stoichiometric relationship existed between the decrease in dissolved iron and the iodine content in this series of samples.

A solution of ferrous iodide in water was next prepared from card teeth and U.S.P. iodine in the usual fashion with the following precautions: (a) Water used in the preparation of the solution was boiled vigorously for 1 hour and cooled in a tightly-stoppered flask; The card teeth used in the preparation were dried in a dessicator and heated to 90° C. for 12 hours to drive off adsorbed air; (b) At the expiration of the reaction, the mixture was boiled vigorously for 20 minutes with occasional shaking; and (c) the solution was poured into pycnometer flasks while still warm and necks of the pycnometers repeatedly immersed in melted paraffin until well coated. A sample

of the solution when analyzed was found to conform to the U.S.P. strength for Syrup of Ferrous Iodide and the pH was 3.1 to La Motte yellow. A sample of this solution when exposed to air, showed the presence of free iodine in 15 minutes.

In contrast to the samples previously considered, this solution did not precipitate in the pycnometers and the iodine content remained very low. No loss of ferrous iron could be detected. Data follow:

Table 25.

Molarity Ratio of Iron and Iodine in the Absence of Oxygen.

Hours	Fe^{++} loss mols/L.	I_2 mols/L.
0	0	0
216	0	0.000438
816	0	0.000489
1127	0	0.000497

The solutions were tested for ferric iron with negative results in every case. It was concluded that little or no decomposition occurred in ferrous iodide solutions which contain a minimum of oxygen and that no stoichiometric relationship is evidenced by these samples.

As indicated in Tables 22, 23 and 24, the ratio of the

loss of molarity of ferrous iron to the gain in molarity of iodine varies inversely with the time of exposure for samples of ferrous iodide solutions exposed to air and tends to attain a limiting value at about 3 mols of ferrous iron loss per mol of iodine formed. Likewise, the average of the two solutions is in good agreement. On the other hand, similar data on a series of solutions in which decomposition ceased upon expiration of air, show a uniformly higher loss of ferrous iron per mol of iodine. It appears strongly probable, in view of these data, that since no soluble ferric compound is formed, a slightly insoluble basic ferrous iodide of variable composition first precipitates and in turn is gradually converted to ferric hydroxide, equilibrium being attained at a value of approximately 3 mols loss of ferrous iron per mol of iodine liberated.

In an attempt to determine the composition of the precipitate formed in the decomposition of samples containing only small quantities of air, samples of the precipitate obtained from the solutions mentioned in Table 24 were filtered off and examined. Certain of these precipitates were washed with alcohol, others with acetone or distilled water, the latter being used in all cases for final washing, and the precipitate was kept covered with solvent as nearly as possible at all times. The general procedure

used was as follows: After filtration, the precipitate was washed with solvent until free from iodide and iodine, transferred to a beaker containing 50 cc. of U.S.P. Diluted Sulphuric Acid, dissolved therein and two 10 cc. samples pipetted off. One sample was analyzed for ferrous iron with permanganate and the other titrated with potassium thiocyanate, after the addition of an excess of silver nitrate T.S., using ferric alum as the indicator. Data follow in Table 26.

Table 26.

Analysis of Precipitates.

Hours	Ferrous iron	Iodide	Precipitate
0	-----	-----	---------
90	1.84×10^{-3}	3.71×10^{-3}	Basic iodide of iron.
138	None	None	Ferric Hydroxide.
214	2.16×10^{-3}	8.45×10^{-5}	Basic iodide of iron.
266	None	None	Ferric Hydroxide.
310	None	None	Ferric Hydroxide.
358	None	None	Ferric Hydroxide.
410	None	None	Ferric Hydroxide.
531	None	None	Ferric Hydroxide.
603	None	None	Ferric Hydroxide.
718	None	None	Ferric Hydroxide.
866	None	None	Ferric Hydroxide.

Table 26 - cont.

Analysis of Precipitates.

Hours	Ferrous iron	Iodide	Precipitate
1126	None	None	Ferric Hydroxide.
1486	None	None	Ferric Hydroxide.
2402	None	None	Ferric Hydroxide.
3122	None	None	Ferric Hydroxide.

As indicated in Table 26, some indications exist for the supposition that a basic iodide of iron is formed early in the decomposition. The statement that the precipitate is composed of ferric hydroxide is based upon the negative tests obtained for ferrous iron and iodine and positive reactions with potassium ferrocyanide T.S. containing a trace of acetic acid. The 266 and 310 hour samples mentioned in the above table, were filtered, the precipitate dried and weighed, ignited and weighed as ferric oxide. Results showed the precipitate to consist entirely of ferric hydroxide.

It has been shown that no apparent stoichiometric relationship exists in the decomposition of ferrous iodide solutions, but if we now consider the appearance of free iodine as due to the oxidation of iodide ion, the mechanism can be shown.

It has been shown that the hydrolysis of ferrous iodide solutions occurs in two stages

(I) $FeI_2 + H_2O \rightleftharpoons Fe(OH)I + H^+ + I^-$

(II) $FeI_2 + 2\ H_2O \rightleftharpoons Fe(OH)_2 + 2\ H^+ + 2\ I^-$

in which the former predominates. Furthermore, it is known that iodide ion is oxidized according to the equation

(III) $2\ I^- + \frac{1}{2}\ O_2 + 2\ H^+ \rightleftharpoons I_2 + H_2O$

and that hydriodic acid decomposes spontaneously according to the equation

(IV) $2\ H^+ + 2\ I^- \rightleftharpoons I_2 + H_2$

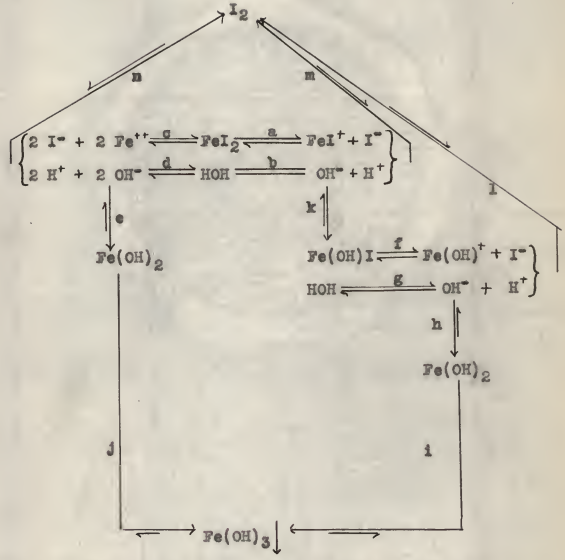
On the other hand, ferrous hydroxide is easily oxidized to ferric hydroxide, a reaction which may be represented ionically

(V) $Fe^{++} + H^+ + \frac{1}{2}\ O_2 \rightleftharpoons 2\ Fe^{+++} + OH^-$

Thus if we assume the decomposition of aqueous solutions of ferrous iodide to be essentially due to oxidation of the products of hydrolysis, it is obvious that no stoichiometric relation need exist, but rather any relationships which are present will be dependent upon the ease of oxidation of the respective ions, i.e., to their respective oxidation-reduction potentials, upon the concentrations of the reacting substances, and upon the insolubility, reactivity or volatility of the products of reaction. This mechanism of decomposition may be represented in one system as follows:

Fig. 2

Chart showing the Mechanism of Decomposition of Aqueous Solutions of Ferrous Iodide.



Note: Small letters are used to identify the various equations making up the above system for convenience in the discussion on pages 150-152.

The mechanism of decomposition of aqueous solutions of ferrous iodide shown in Fig. 2, page 149, as derived from experimental data, lends itself admirably to an explanation of all observed data or vice versa.

1. In the manufacture of solutions of ferrous iodide, primary equilibrium may be considered as consisting of the hydrolysis reactions a, b, c, d, e and k, while secondary equilibrium is more slowly attained due to the heterogeneity occasioned by partial precipitation of the basic salt, thus slowing reactions f, g and h, which are necessary for secondary equilibrium. In addition, it may be assumed that the carbon in card teeth adsorbs the precipitate of basic salt during the reaction in manufacture thus facilitating secondary hydrolysis and resulting in a pH of 3.1,i.e., reactions f, g and h occur.

2. It has been noted that solutions of ferrous iodide continue to precipitate over long periods without simultaneous increase in acidity after secondary equilibrium has been attained. Reactions c, d, and e have been shown to occur only to a very slight extent, thus making it probable that precipitation of ferric hydroxide may occur as a result of reaction j without perceptibly lowering the pH of the solution as determined colorimetrically.

3. Since reactions a, b and k predominate in the

solution, it is logical to expect reaction m to furnish most of the free iodine formed. Since oxidation-reduction potentials show that oxygen oxidizes iodide ion to iodine more readily than ferrous to ferric iron, it is also logical to expect more mols of iodine to be formed than of ferric hydroxide despite the insolubility of the latter.

4. Considering the data in Table 25, it is seen that while some iodine appeared in the solutions, no loss of ferrous iron was recorded. This is compatible with the theory as well as with the oxidation-reduction potentials. Assuming the solubility of air in solutions of ferrous iodide to be the same as in water at 25° C, 1000 cc. of water will contain 17.08 cc. of air which in turn contains 33.82 % oxygen, or a total of 5.776 cc. of dissolved O_2 (284). Reducing this value to 0° C. at atmospheric pressure, 25 cc. of the solution in the pycnometers will contain 0.144 cc. of oxygen weighing 0.00142 gram per cc., or a total of 0.000188 gram of oxygen. Since 16 grams of oxygen are required to react with each mol of ferrous iron on the stoichiometric basis, the weight of oxygen divided by 16 represents the number of mols of ferric iron which may be formed in the pycnometers. This value is 0.0000117 mole. Likewise, if we assume that any hydriodic acid formed (equation I, p 136) is completely decomposed, this amount

of oxygen will account for total of 0.0000117 mols of iodine formed in the solution. Multiplying this value by 40, to transform it to mols per liter, we find that the dissolved oxygen will account for the formation of 4.70×10^{-4} mols per liter of iodine, whereas actually 4.97×10^{-4} mols/L. were formed at the end of 1127 hours. These data are, of course, inconclusive; nevertheless, in view of the fact that Husa and Shattuck (285) have shown that solutions of hydriodic acid decompose to a greater extent than can be accounted for on the basis of dissolved oxygen, they are of significance as verifying to some extent the mechanism of the reaction here advanced.

As further verification of this mechanism, an experiment was performed, based on the work of Husa and Shattuck (285), who showed that additional iodide ion as well as excess ferrous ion increased the rate of decomposition of hydriodic acid. It was reasoned that since the oxidation of hydriodic acid is of necessity a case of iodide ion oxidation, the addition of ions such as were used by Husa and Shattuck to ferrous iodide solutions should increase the rate of decomposition if the mechanism were correct. The data in Table 27 represent the results of this experiment. Three samples of solution of ferrous iodide, prepared in the usual fashion and stored in pyrex bottles

in darkness, were assayed frequently. The first solution was used as a control, the second contained 1 mol of added potassium iodide per liter of solution and the third contained 0.22 mol per liter of ferrous sulfate. All chemicals were of Reagent grade except the potassium iodide which was Merck's C.P. chemical.

Table 27.

Effect of the Addition of Excess Ions.

	mols /L. of iodine in:		
Ion in excess	47 hours.	193 hours.	841 hours.
Control	7.34×10^{-4}	2.72×10^{-3}	1.32×10^{-2}
Ferrous ion	7.58×10^{-4}	3.53×10^{-3}	1.93×10^{-2}
Iodide ion	6.75×10^{-4}	3.32×10^{-3}	2.56×10^{-2}

As indicated in Table 27, an excess of either iodide ion or ferrous ion increased the rate of decomposition of solutions of ferrous iodide. Thus, it was concluded that according to the explanation offered by Husa and Shattuck of this phenomenon, these data offer further evidence in support of the mechanism of decomposition herein advanced.

It was concluded that the best explanation of the decomposition of aqueous solutions of ferrous iodide depends upon assuming oxidation of iodide ion formed by

the hydrolysis of the salt.

The Rate of Decomposition of Ferrous Iodide Solutions. In order to compare the action of preservatives with each other and with the unstabilized solution of ferrous iodide, it was found desirable to determine specific reaction rates in each case. Since iodide ion is known to be photosensitive to oxidation, reaction rates were determined in the dark.

Winther (286) stated that the oxidation of iodide ion in the dark is a combination of oxidation of iodide ion at constant velocity and oxidation of I_3^- ion at a velocity proportional to the iodine concentration. The work of Plotnikoff (184) has already been discussed (p 58-62) but is not directly applicable, since his value of the specific reaction rate is admittedly limited to relatively high hydrogen ion concentrations. Other authorities (287) stated the decomposition of hydriodic acid to be bimolecular at high temperature and unimolecular when photochemical.

For the purpose of this work, a solution of ferrous iodide was prepared from Reagent iron and Reagent iodine and stored in the thermostat in darkness at 30° C. in a container with an excess of oxygen, the progress of the decomposition being followed by titrating the free iodine formed with approximately 0.01 N. sodium thiosulfate

solution. Preliminary experiments showed that the rate of decomposition in black or colorless bottles placed in various parts of the thermostat were identical but that the type of glass affected the rate of decomposition, glass conferring alkalinity to distilled water having a decelerating effect upon the decomposition. For the purpose of this work, containers which corresponded to the alkalinity shown by prescription bottles were used as offering data most pertinent for pharmaceutical purposes. Specific reaction rates, i.e., the percentage of substance reacting in unit of time, were calculated from the observed data by means of the first and second order velocity equations (288):

$$(I)\quad K_m = \frac{2.303}{t} \log \frac{a}{a - x}$$

$$(II)\quad K_b = \frac{1}{t} \cdot \frac{x}{a\,(a-x)}$$

where K_m represents the specific reaction rate as calculated for a reaction of the first order and K_b represents that for a second order reaction. The fraction decomposed in time t is represented by x, and the initial concentration by a. All calculations of these constants are based entirely upon total iodide thus regarding the concentration of oxygen as sufficiently large in the solution to be considered a constant value.

The data as obtained from the solution described above follow in Tables 28 and 29. Column I shows the total hours storage, column II shows the elapsed time between determinations, column IX represents the value of a in equations (I) and (II) after subtraction of x , the amount decomposed. All calculations of K_m and K_b are based upon the total concentration of iodide rather than that portion ionized, using segment hours for all values of t . The symbol D or PD indicates that the solution was either decolorized or partially decolorized with sodium thiosulfate before a colorimetric pH could be taken. This procedure was validated by determining the pH of freshly prepared ferrous iodide solutions, adding iodine, decolorizing as above and redetermining the pH; no change could be detected colorimetrically. Data follow:

Table 28.

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Reagent Iron and Reagent Iodine.

I Total hours	II Segment hours	III Gm./L. iodide.	IV mols/L. iodide	V Ferrous iron Gm./L.	VI Ferrous iron mols/L.
0	0	70.5268	.22710	13.111	.2348
95	95	70.2152	.22672	13.145	.2354
148½	53½	70.2523	.22648	13.111	.2348
215	66½	70.5268	.22710	13.033	.2334
263	48	70.2400	.22680	12.530	.2244

Table 28 - cont.

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Reagent Iron and Reagent Iodine.

I Total hours	II Segment hours	III Gm./L. iodide.	IV mols/L. iodide.	V Ferrous iron Gm./L.	VI Ferrous iron mols/L.
315½	52½	70.2152	.22672	12.637	.2263
359	43½	70.2400	.22680	12.637	.2263
411	52	70.1601	.22651	12.637	.2263
532	121	70.2833	.22694	12.530	.2244
719	187	70.1354	.22643	12.058	.2159
863	144	70.1354	.22643	12.089	.2165
1123	260	70.0541	.22620	12.037	.2155
1483	360	70.2400	.22679	11.692	.2094
2400	917	70.2493	.22683	11.460	.2052
3120	720	70.1749	.22659	11.185	.2003

Table 29.

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Reagent Iron and Reagent Iodine.

VII Iodine Gm./L.	VIII Iodine mols/L. x 10^3	IX Conc. (a-x) mols/L.	X $K_m \times 10^5$	XI $K_b \times 10^4$	XII pH
0.0000	0.000	.22672	----	----	4.1
0.2228	0.870	.22585	4.05	1.79	3.2
0.3104	1.22	.22550	1.51	4.46	3.2
0.3622	1.43	.22529	1.06	4.20	3.2

Table 29 - cont.

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Reagent Iron and Reagent Iodine.

VII Iodine Gm./L.	VIII Iodine mols/L. x 10^3	IX Conc. (a-x) mols/L.	X K_m x 10^5	XI K_b x 10^4	XII pH
0.4139	1.63	.22509	.98	6.65	3.2
0.4646	1.83	.22489	1.74	6.86	3.2
0.5052	1.99	.22473	1.74	8.98	3.2
0.6898	2.72	.22400	1.80	10.29	3.2
0.8657	3.41	.22331	1.32	5.57	3.2
1.1313	4.46	.22226	1.29	4.73	3.2 D
1.2765	5.03	.22169	1.76	6.95	3.1 D
1.6211	6.38	.22033	2.38	4.92	3.1 D
2.0040	7.89	.21883	1.89	4.42	3.1 D
2.9320	11.55	.21517	1.84	2.60	3.1 D
3.643	14.35	.21237	1.82	4.14	3.1 D
		Average	1.79		

As shown in Tables 28 and 29, the total iodide remained reasonably constant over a period of 3120 hours. The ferrous iron content decreased steadily, the total loss being nearly twice as great as the free iodine found present. The pH attained the usual secondary equilibrium, precipitation accompanying the increased acidity. It will be seen that the values of K_m are in much better agreement

than those of K_b and it is of interest to note that the rate of decomposition was nearly 4 times as rapid as measured by K_m during the earliest stage of decomposition, than later after secondary equilibrium was attained.

In order to determine the effect exerted by the impurities present in card teeth, a solution was prepared from card teeth and Reagent iodine and stored as above, care being taken to use a container such that the same surface exposure would result as in the case of the Reagent iron sample. Notation is similar to that in preceding tables.

Table 30.

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Card Teeth and Reagent Iodine.

I Total hours	II Segment hours	III Gm./L. iodide.	IV mols/L. iodide.	V Ferrous iron Gm./L.	VI Ferrous iron mols/L.
0	0	69.931	.22580	12.924	.23145
73	73	69.975	.22588	12.920	.23137
121	48	69.820	.22584	12.735	.22806
172.5	51.5	70.078	.22541	12.493	.22373
240	67.5	70.076	.22628	12.478	.22346
292	52	69.954	.22588	12531	.22440
340	48	69.845	.22553	12.531	.22440
384	44	70.178	.22660	12.531	.22440

Table 30 - cont.

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Card Teeth and Reagent Iodine.

I Total hours	II Segment hours	III Gm./L. iodide	IV mols/L. iodide.	V Ferrous iron Gm./L.	VI Ferrous iron mols/L.
436	52	69.943	.22585	12.320	.22060
557	121	69.975	.22594	12.022	.21530
774	217	69.941	.22584	11.754	.21051
918	144	69.875	.22562	11.817	.21162
1178	260	69.940	.22584	11.754	.21051
1538	360	70.078	.22628	10.873	.19470
1838	300	70.046	.22618	10.873	.19470
2158	320	69.945	.22585	9.846	.17632
2455	277	69.952	.22587	9.823	.17590
3007	552	69.998	.22602	8.438	.15111
Average		69.975	.22594		

Table 31

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Card Teeth and Reagent Iodine.

VII Iodine Gm./L.	VIII Iodine mols/L. x 10^3	IX Conc. (a-x) mols/L.	X $K_m \times 10^5$	XI $K_b \times 10^4$	XII pH
0.0000	0.000	.22594	-----	-----	3.3
0.0148	0.058	.22588	0.379	0.156	3.4

Table 31 - cont.

Rate of Decomposition of Ferrous Iodide Solutions Prepared from Card Teeth and Reagent Iodine.

VII Iodine Gm./L.	VIII Iodine mols/L. x 10^3	IX Conc. (a-x) mols/L.	X $K_m \times 10^5$	XI $K_b \times 10^4$	XII pH	
0.0262	0.103	.22584	0.384	0.427	3.4	
0.1353	0.533	.22541	3.71	2.03	3.4	
0.2506	0.987	.22495	3.00	2.88	3.3	
0.3402	1.34	.22460	3.01	5.11	3.3	
0.4316	1.70	.22424	3.32	7.03	3.2	
0.5204	2.05	.22389	3.61	9.28	3.2	
0.6347	2.50	.22344	3.85	9.61	3.2	
0.7641	3.01	.22293	3.37	5.00	3.1	
1.262	4.98	.22096	3.26	4.66	3.0	PD
1.526	6.01	.21993	3.26	8.58	3.1	PD
1.998	7.87	.21797	3.44	6.31	3.1	PD
2.699	10.63	.21531	3.41	6.29	3.1	PD
3.252	12.81	.21313	3.39	9.30	3.1	PD
3.818	15.04	.21090	3.28	10.4	3.1	PD
4.318	17.01	.20893	3.40	13.9	3.1	PD
5.288	20.83	.20511	3.34	8.80	3.1	PD
		Average	3.22			

As in the preceding case, the data in Tables 30 and 31 show good agreement for the first order reaction constant

K_m. It is noted, however, that this is nearly twice as great as in the case of the Reagent iron sample, 0.00322 % of the total iodide present at any time t, being decomposed per hour. The loss of ferrous iron is approximately 4 times as great as the quantity of iodine present. It is also evident that a short period of induction, a phenomenon commonly associated with catalytic reactions, during which decomposition had not yet reached maximum rate, occurred in this case.

It has been shown (289) that the rusting of iron is favored by (a) impurities in the metal; (b) contact with more noble metals; (c) the presence of moisture; (d) the presence of carbon dioxide; and (e) oxygen. The first two factors facilitate the production of galvanic elements; the third is necessary for current conduction. In an attempt to account for the relatively greater loss of iron in the card teeth sample, a qualitative analysis for the common elements was performed according to the method of A. A. Noyes (290). Carbon, sulfur and silicon were found present with the presence of manganese questionable. It was concluded that the relatively greater loss of ferrous iron in this case was due to the minute quantities of dissolved impurity.

Taylor (291) states that the "Measurement of the rate

of reaction is a valuable method for the determination of its mechanism. This may be most conveniently done by the substitution of data into the velocity formulas and thus finding sets of values for K. When using this method, it is important to do several experiments using different concentrations of the reactants, i.e., different concentrations may not agree upon a value for one order of reaction, but may agree upon a value for a reaction of different order". He also states that opposing or side reactions, when present, render it necessary to confine measurements to the early stages of the reaction when only small quantities of the reactants disappear. The precision of the calculated constants is, however, in this case not so good.

In accordance with the method outlined by Taylor, two samples of a solution prepared from card teeth[1] and Reagent iodine and of different concentrations were stored in the thermostat under the conditions previously outlined for such experiments. The data in Tables 32 and 33 represent the values of K_m and K_b for a solution 0.47935 molar in ferrous iodide.

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1. Card teeth were chosen for these experiments since the data so obtained are more nearly applicable to pharmaceuticals, this form of iron being the most widely used for this purpose.

Table 32.

Rate of Decomposition for Card Teeth Solution 0.47935 molar in Ferrous Iodide.

Total hours	Segment hours	Iodide mols/L.	pH	
0	0	0.48003	2.9	
120	120	0.47846	3.2	
288	168	0.47867	2.9	
388	120	0.47935	2.9	
642½	254½	0.47981	2.8	PD
1007	364½	0.48003	2.8	PD
1559½	552½	0.47906	2.8	PD
2040	480½	0.47935	2.8	PD
2520	480	0.47944	2.8	PD
3048	528	0.47930	2.8	PD
	Average	0.47935		

Table 33.

Rate of Decomposition for Card Teeth Solution 0.47935 molar in Ferrous Iodide.

Iodine mols/L. x 10^2	Conc. (a-x) mols/L.	$K_m \times 10^5$	$K_b \times 10^5$
0.000	0.47935	-----	-----
0.215	0.47720	3.76	7.82
0.442	0.47493	2.85	11.61
0.706	0.47299	3.41	26.19

Table 33 - cont.

Rate of Decomposition for Card Teeth Solution 0.47935 molar in Ferrous Iodide.

Iodine mols/L. x 10^2	Conc. (a-x) mols/L.	$K_m \times 10^5$	$K_b \times 10^5$
0.991	0.46944	2.96	17.54
1.493	0.46442	2.95	18.78
2.300	0.45635	3.17	19.64
3.020	0.44915	3.31	30.87
3.715	0.44220	3.25	38.97
4.460	0.43475	3.22	43.94
	Average	3.21	

As shown in Tables 32 and 33, the mean of the values of K_m , 3.21 x 10^{-5}, is in strikingly good agreement with that found for a sample approximately half this strength, i.e., 3.22 x 10^{-5}.

A sample was next prepared from card teeth and Reagent iodine and stored under conditions identical with the preceding samples. The strength was so regulated that the concentration was only approximately half that of the regular sample as tabulated in Tables 30 and 31, or about one-fourth that of the sample as tabulated in Tables 32 and 33. Data follow:

Table 34.

Rate of Decomposition for Card Teeth Solution 0.1177 molar in Ferrous Iodide.

Total hours	Segment hours	Iodide mols/L.	pH
0	0	0.1187	4.3
120	120	0.1142	3.4
360	240	0.1169	3.4
790	430	0.1192	3.4
1510	720	0.1181	3.5
2086	576	0.1189	3.4
	Average	0.1177	

Table 35.

Rate of Decomposition for Card Teeth Solution 0.1177 molar in Ferrous Iodide.

Iodine mols/L. x 10^2	Conc. (a-x) mols/L.	$K_m \times 10^5$	$K_b \times 10^5$
0.000	0.1177	-----	-----
0.061	0.1171	4.36	3.69
0.162	0.1160	3.61	49.7
0.348	0.1142	3.75	61.1
0.657	0.1111	3.82	71.9
0.903	0.1086	3.85	129.9
	Average	3.88	

As shown in this tabulation, the iodide content remained approximately constant throughout, the values of K_b are in poor agreement while those of K_m are relatively good in this respect. The mean of the values of K_m, while not in as good agreement with the other two cases as might be expected, are well within the limits of experimental error. Thus it was concluded from these data that the rate of reaction for the decomposition of solutions of ferrous iodide may be calculated from the first order velocity equation in cases where oxygen is present in excess, the specific reaction rate being greater in the case of card teeth samples than in the case of Reagent iron samples.

It has been suggested by Krantz (p 39) that the rate of decomposition is in direct proportion to the area of surface exposed, in other words, that the reaction is one of the zero order and depends upon the rate of infiltration of oxygen, a factor which in turn depends upon the surface exposed. In order to test this point, a sample prepared from card teeth was stored as usual but in a container of such type that only a fraction of the surface previously exposed was allowed access to the air. Data follow in Tables 36 and 37.

Table 36.

Rate of Decomposition of Card Teeth Solution with Restricted Exposure to Air.

Total hours	Segment hours	Iodide mols/L.	pH
0	0	0.22951	3.2
121	121	0.22926	3.2
287½	166½	0.22914	3.1
450½	163	0.22945	3.1
666½	216	0.22938	3.1
1009	342½	0.22944	3.1
1561	552	0.22951	3.1
1686	124	0.22943	3.1
2386	720	0.22950	3.1
2506	120	0.22958	3.1
2986	480	0.22922	3.1
	Average	0.22940	

Table 37.

Rate of Decomposition of Card Teeth Solution with Restricted Exposure to Air.

Iodine mols/L. x 10^3	Conc. (a-x) mols/L.	$K_m \times 10^5$
0.000	0.22940	------
0.903	0.22850	3.24
1.77	0.22763	2.30

Table 37 - cont.

Rate of Decomposition of Card Teeth Solution with Restricted Exposure to Air.

Iodine mols/L. x 10^3	Conc. (a-x) mols/L.	$K_m \times 10^5$
3.03	0.22637	3.41
4.28	0.22512	2.56
6.99	0.22241	3.54
11.01	0.21839	3.30
11.90	0.21750	3.30
16.97	0.21243	3.28
17.81	0.21159	3.28
21.14	0.20826	3.31
	Average	3.15

It was concluded from the data in Tables 36 and 37, that the area of surface exposed had little effect upon the rate of reaction. Similarly, it appears probable that the reaction, under ordinary circumstances of exposure to air is not of the zero order, but instead, that sufficient oxygen is usually contained in the solution to allow the reaction to proceed, i.e., absorption is usually more rapid than reaction.

Factors Affecting the Rate of Decomposition. The U.S.P. X directs that Syrup of Ferrous Iodide be stored in

"completely filled, tightly-stoppered bottles"; other investigators (36, 77, 113) have stated that the preparation should be kept in bright sunlight; and Krantz (130) showed that very viscous solutions were resistant to oxidation by hydrogen peroxide. In order to obtain information regarding the three factors air, light and viscosity as well as a fourth, variations in temperature, a series of experiments was undertaken so designed as to evaluate these factors.

A. The influence of viscosity. In order to measure the effect of viscosity upon the specific reaction rate, solutions of ferrous iodide of a strength corresponding to that of the U.S.P. syrup were prepared from card teeth, sufficient 1-10 mucilage of tragacanth[1] added to produce the desired viscosity and the solution stored in the presence of excess air in the thermostat at 30° C. The viscosity was determined by the viscosimeter method (292), and the progress of the reaction followed by titration of the iodine formed with approximately 0.01 N thiosulfate solution. The pH value of all solutions was approximately

1. Tragacanth was chosen for this purpose because its solutions are neutral and it is a carbohydrate. Although it is probable that results obtained are directly dependent upon viscosity, the possibility exists that some other factor, proportional to the viscosity, controls the rate of oxidation.

3.0 to 3.1 although determinations were rendered difficult by the presence of the gum. The calculations of the specific reaction rate, K_m, have been explained above.

As a preliminary experiment to show that tragacanth is without action upon iodine, 50 cc. of 1-10 mucilage of tragacanth was added to enough water to make 250 cc., sufficient U.S.P. Compound Solution of Iodine added to make the solution approximately 0.02 N, and portions of the solution stored in glass-stoppered bottles containing excess air in the refrigerator at approximately 6° C., in the thermostat at 30° C., and in the electric oven at approximately 50° C. The results of analyses for total iodine at various intervals follow in Table 40.

Table 40.

The Action of Tragacanth on Iodine.

Temperature	Time in hours:			
	0	300	552	1027
50° C.	0.01001	0.01000	0.01009	0.01004
30° C.	0.01001	0.01007	0.01013	0.01011
6° C.	0.01001	0.01017	0.00996	0.01011

It was concluded from these data that tragacanth is without effect upon iodine in dilute solutions between 6° C. and 50° C. after the expiration of 1027 hours.

The data shown in Table 41 represent the results of analyses and calculations of the specific reaction rates for a solution of ferrous iodide prepared from card teeth and having a relative viscosity of 2.507 at 30° C. relative to water at the same temperature. The solution was 0.22811 molar with respect to ferrous iodide.

Table 41.

Rate of Decomposition of Solution of Ferrous Iodide at 30° C.

Relative Viscosity 2.507.

Hours		Iodine	Concentration	$K_m \times 10^5$
Total	Segment	mols/L. $\times 10^3$	mols/L. (a-x)	
0	0	----	0.22811	-----
312	312	1.184	0.22693	1.67
552	240	2.213	0.22590	1.89
744	192	2.901	0.22521	1.60
984	240	3.814	0.22430	1.69
1227	243	4.793	0.22332	1.80
			Average	1.73

Similar data as obtained from a solution having a relative viscosity of 6.296 at 30° C. relative to water at the same temperature are given in Table 42. The solution was 0.22783 molar in ferrous iodide.

Table 42.

Rate of Decomposition of Solution of Ferrous Iodide at 30° C.

Relative Viscosity 6.296

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	$K_m \times 10^5$
0	0	----	0.22783	----
312	312	0.734	0.22710	1.03
552	240	1.271	0.22656	1.00
744	192	1.709	0.22612	1.01
984	240	2.252	0.22558	1.00
1227	243	2.815	0.22502	1.02
			Average	1.01

Similar data as obtained from a solution having a relative viscosity of 19.8 at 30° C. relative to water at the same temperature are shown in Table 43. The solution was 0.21323 molar with respect to ferrous iodide.

Table 43.

Rate of Decomposition of Solution of Ferrous Iodide at 30° C.

Relative Viscosity 19.8

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	$K_m \times 10^5$
0	0	----	0.21323	-----
120	120	0.24	0.21299	0.96

Table 43 - cont.

Rate of Decomposition of Solution of Ferrous Iodide at 30° C.

Relative Viscosity 19.8.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
480	360	1.07	0.21216	1.07
1200	720	2.84	0.21039	1.16
1320	120	3.08	0.21015	0.99
1848	528	4.29	0.20894	1.08
			Average	1.05

Similar data as obtained from a solution having a relative viscosity of 539.7 at 30° C. relative to water at the same temperature are shown in Table 44. The solution was 0.21490 molar with respect to ferrous iodide.

Table 44.

Rate of Decomposition of Solution of Ferrous Iodide at 30° C.

Relative Viscosity 539.7.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
0	0	----	0.21490	-----
120	120	0.214	0.21469	0.81
480	360	0.812	0.21409	0.78
1200	720	1.98	0.21292	0.76

Table 44 - cont.

Rate of Decomposition of Solution of Ferrous Iodide at 80° C.

Relative Viscosity 539.7.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
1320	120	2.18	0.21272	0.79
1848	528	3.09	0.21181	0.81
			Average	0.79

A summary of the data contained in Tables 31 and 41 to 44 inclusive appears in Table 45.

Table 45.

The Effect of Viscosity upon the Rate of Decomposition of Solutions of Ferrous Iodide.

Viscosity (poises)	Viscosity (relative)	K_m
0.009593	1.072	3.22 x 10^{-5}
0.022440	2.507	1.73 x 10^{-5}
0.055070	6.296	1.01 x 10^{-5}
0.177200	19.80	1.05 x 10^{-5}
4.830	539.7	0.79 x 10^{-5}

As shown by the preceding data, the rate of decomposition decreases with increasing viscosity, the greatest decrease lying between relative viscosities of 1 and 6;

increases in viscosity beyond a relative viscosity of 6 are of no appreciable value in decreasing the rate of decomposition. The data from Table 45 are graphed (p 177) and it is evident that the specific reaction rate, K_m, is a hyperbolic function of the viscosity, or of some factor proportional to the viscosity of the solution.

B. The effect of variations in temperature. It is well known that most chemical reactions approximately double or treble in their rate of reaction for each ten degree rise in temperature. In order to evaluate this temperature coefficient in the case of ferrous iodide solutions of various viscosities, a solution was first prepared and placed in an electric oven at approximately 50° C. The solution was prepared from card teeth and U.S.P. iodine and stored in a container with an excess of air. The solution assayed 0.22690 mols per liter of total iodide; the pH was 3.2. Data follow in Table 46, page 178.

Fig. 3

Graph showing the Effect of Viscosity upon the Specific Reaction Rate in the Decomposition of Aqueous Solutions of Ferrous Iodide at 30° C. Data plotted from Table 45 (page 176).

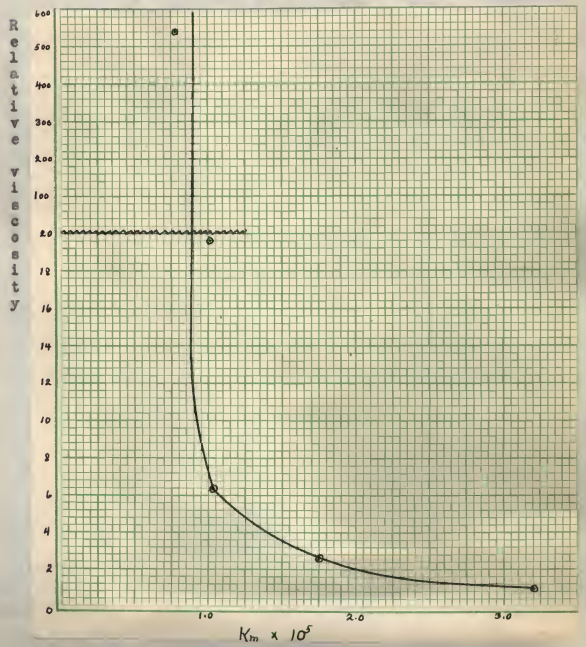


Table 46.

Rate of Decomposition of Solution of Ferrous Iodide at 50° C.

Hours Total	Hours Segment	Iodine mols/L. x 10^2	Concentration mols/L. (a-x)	K_m x 10^4
0	0	-----	0.22690	-----
47½	47½	0.312	0.22378	2.93
166½	119	1.343	0.21347	3.66
215	48½	1.644	0.21046	2.97
335	120	2.424	0.20266	3.14
575	240	3.986	0.18704	3.34
			Average	3.21

As shown in Table 46, the value of K_m, i.e., 3.21 x 10^{-4}, is almost exactly ten times as great as the value obtained at 30° C., i.e., 3.22 x 10^{-5}. It was concluded that the temperature coefficient for solutions of ferrous iodide between 30° and 50° C. is approximately three for each ten degree rise in temperature.

A solution similar in every respect to that placed in the oven as above described, was placed in the refrigerator at about 6° C. and frequently analyzed. Excess air was present in the container. Data follow in Table 47.

Table 47.

Rate of Decomposition of Solution of Ferrous Iodide at 6° C.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5	Ppt.
0	0	----	0.22690	----	No
47½	47½	0.450	0.22645	4.39	No
192½	145	1.422	0.22548	2.97	No
548½	356	4.513	0.22239	3.88	Ppt.
772	219½	6.396	0.22050	3.88	Ppt.
1012	240	8.400	0.21850	3.81	Ppt.
			Average	3.78	

Due to the unexpected results shown by the data in Table 47, they were checked with a second series taken from another sample. Concordant results, however, were obtained. A possible explanation for this unusual behavior depends on the fact that at low temperatures oxygen is sufficiently more soluble to allow the reaction to proceed, due to greater concentration of one ingredient, more rapidly than would be expected.

It is shown in Table 47, that precipitation did not occur in this sample until the expiration of 145 hours. Since the pH of the solution was 3.2, the pOH was 10.8 and the hydroxyl ion concentration was 1.59×10^{-9}. At this

point, there had decomposed 4.501 x 10^{-4} mols per liter of ferrous iodide, and on the stoichiometric basis,

$$FeI_2 + H_2O + \tfrac{1}{2} O_2 \rightleftharpoons Fe(OH)_3 + HI + \tfrac{1}{2} I_2$$

there would have been formed for each mol of iodine, 2 mols of ferric hydroxide or 2.842 x 10^{-4} mols per liter of ferric ion. The concentration of ferric hydroxide in the solution at this pOH would then be given by the expression:

$$(2.842 \times 10^{-4})(1.59 \times 10^{-9})^3 = 1.142 \times 10^{-30}$$

Since this value exceeds the solubility product by about 1,000,000 times, it is evident that precipitation should have occurred before this time. This, however, is easily accounted for on the basis of the mechanism of decomposition previously advanced and the facts are listed here as further substantiation of that mechanism.

In order to evaluate the heat coefficient in more viscous solutions, ferrous iodide solutions rendered viscous by the addition of tragacanth, were stored in the oven and in the refrigerator and the rate of decomposition and the viscosity noted at those temperatures.

The data tabulated in Table 48 represent the results of analyses performed upon a solution of ferrous iodide having a relative viscosity of 1.200 at 50° C. compared to water at 30° C. and containing 0.22525 mols per liter of ferrous iodide. It was maintained at 50° C. in the

electric oven in the presence of excess air.

Table 48.

Rate of Decomposition of Solution of Ferrous Iodide at 50° C.

Relative Viscosity 1.20.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	$K_m \times 10^5$
0	0	-----	0.22525	-----
68	68	2.120	0.22313	12.53
405	337	7.438	0.21781	7.46
648	243	11.52	0.21373	7.79
885	237	15.19	0.21006	7.31
1125	240	18.89	0.20636	7.41
			Average	8.50

The data tabulated in Table 49 represent the results of analyses performed upon a solution of ferrous iodide having a relative viscosity of 26.74 at 50° C. as compared to water at 30° C. All conditions of manufacture, storage and analysis were identical with the above samples.

Table 49.

Rate of Decomposition of Solution of Ferrous Iodide at 50° C.

Relative Viscosity 20.74.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	$K_m \times 10^5$
0	0	-----	0.21223	----
48	48	0.260	0.21197	2.26
264	216	3.341	0.20889	6.82
648	384	8.921	0.20331	7.08
888	240	12.31	0.19992	6.98
1128	240	15.69	0.19654	7.11
			Average	6.05

As shown by the data in Tables 48 and 49, the samples apparently tend to approach the value 7×10^{-5} as the specific reaction rate although the rate of decomposition as measured in the early stages of decomposition is more nearly in keeping with the result to be expected. It was thought that this effect might be due to the extremely slow solubility of tragacanth, with consequent increases in the viscosity over a period of time, thus providing a solution which became progressively more viscous and causing variations in the rate of reaction from those originally found. In order to verify this statement, two solutions were prepared and stored at 50° C. under the usual conditions, the viscosity being determined at the time of

preparation and at the time of analysis. Data follow in Table 50.

Table 50.

Rate of Decomposition of Solutions of Ferrous Iodide at 50° C

Relative Viscosities 2.26 and 5.13

Hours	Relative Viscosity at 50° referred to water at 30° C.	Iodine mols/L. x 10^3	Concent. mols/L. (a-x)	K_m x 10^5
0	2.26	----	0.22811	-----
336	5.13	4.525	0.22358	5.98
0	5.94	----	0.22383	-----
336	10.53	4.229	0.22360	5.58

As indicated by these data, increases in viscosity occurred, probably due to increased solubility of tragacanth, thus making it necessary to use reaction data obtained in the early stages of the decomposition. Under these conditions, determinations are of necessity subject to considerable error.

In view of the results of the work outlined in Table 50, viscosities were redetermined upon the solutions used to determine reaction rates at 30° C. In no case, however, was a variation noted.

The results obtained in Tables 46, and 48 to 50

inclusive are summarized in Table 51. Early reaction rate data only are used, it being understood that results are only approximate.

Table 51.

Variation of Specific Reaction Rate with Viscosity at 50° C.

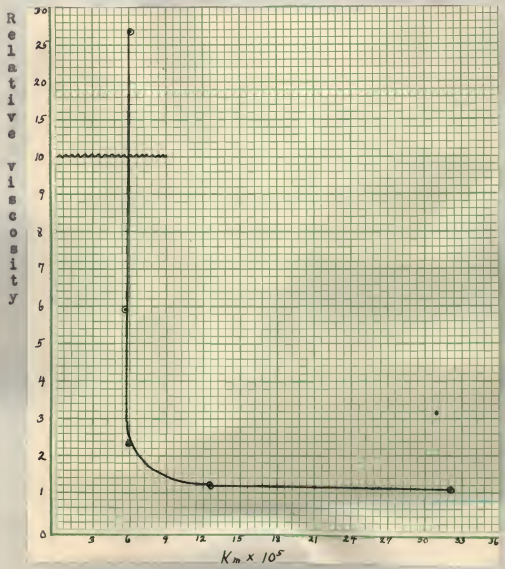
Relative Viscosity	K_m
1.072	3.21×10^{-4}
1.200	1.25×10^{-4}
2.26	5.98×10^{-5}
5.94	5.58×10^{-5}
26.74	6.05×10^{-5}

From the data shown in Table 51 and the graph (Fig. 4, page 185) it was concluded that the variation in specific reaction rate at 50° C. for solutions of ferrous iodide is a hyperbolic function of the viscosity.

In accordance with the plan previously outlined, the rate of deterioration of viscous samples of solution of ferrous iodide stored at 6° C. was determined. Solutions were, without exception, stored in the refrigerator with an excess of air in the container. The data in Table 52 were obtained from a solution having a relative viscosity of 64.32 at 6° C. referred to water at 30° C. Table 53 shows

Fig. 4

Graph showing the Effect of Viscosity upon the Specific Reaction Rate in the Decomposition of Aqueous Solutions of Ferrous Iodide at 50° C. Data plotted from Table 51, (page 184).



similar data for a solution having a relative viscosity of 89.68, and Table 54 illustrates a solution of relative viscosity 525. Data for a solution of indeterminable viscosity, i.e., semisolid in character, is shown in Table 55.

Table 52.

Rate of Decomposition of Solution of Ferrous Iodide at 6° C.

Relative Viscosity 64.32.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
0	0	----	0.22310	----
360	360	1.777	0.22632	2.18
600	240	3.032	0.22507	2.30
840	240	4.221	0.22388	2.22
			Average	2.23

Table 53.

Rate of Decomposition of Solution of Ferrous Iodide at 6° C.

Relative Viscosity 89.68.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
0	0	----	0.22380	------
360	360	0.829	0.22697	1.01
600	240	1.377	0.22642	1.01
840	240	1.974	0.22583	1.09
			Average	1.04

Table 54.

Rate of Decomposition of Solution of Ferrous Iodide at 6° C.

Relative Viscosity 525.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
0	0	-----	0.21077	-----
672	672	3.334	0.20610	3.33
912	240	6.507	0.20426	3.73
1152	240	8.178	0.20259	3.43
			Average	3.50

Table 55.

Rate of Decomposition of Solution of Ferrous Iodide at 6° C.

Relative Viscosity Indeterminable.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
0	0	-----	0.21223	-----
672	672	3.649	0.20858	2.58
912	240	4.843	0.20739	2.38
1152	240	6.134	0.20610	2.60
			Average	2.52

The data as obtained in the preceding tables for the rate of decomposition of solutions of ferrous iodide at 6° C. is summarized in Table 56.

Table 56.

Variation of Specific Reaction Rate with Viscosity for Solutions of Ferrous Iodide at 6° C.

Relative Viscosity	K_m
1.017	3.78×10^{-5}
64.32	2.23×10^{-5}
89.68	1.04×10^{-5}
525.	3.50×10^{-5}
Semi-solid	2.52×10^{-5}

it was concluded from these data and the graph (Fig. 5, page 189) that at 6° C. the specific reaction rate decreases with increase in viscosity up to a relative viscosity of approximately 90.

C. The effect of limited oxygen availability. In order to test the supposition that the solution would decompose only to a very slight extent if air were excluded, a liter of solution prepared from card teeth was stored in completely filled, tightly-stoppered bottles in the thermostat at 30° C. Single bottles were removed at intervals and tested for iodine and total iodine. No positive test was given in any instance for the presence of ferric iron by the use of the thiocyanate test. Data follow:

Fig. 5

Graph showing the Effect of Viscosity upon the Specific Reaction Rate in the Decomposition of Aqueous Solutions of Ferrous Iodide at 6° C. Data plotted from Table 56, (page 188).

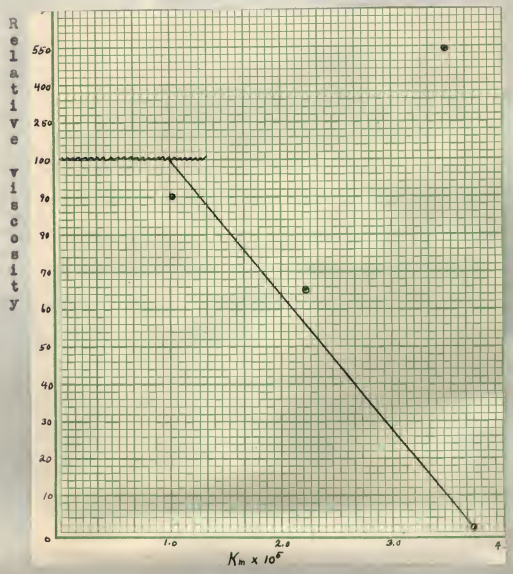


Table 57.

Decomposition of Solutions of Ferrous Iodide in Completely Filled, Tightly-Stoppered Sealed Containers:

Hours	Iodide mols/L.	Ferrous iron mols/L.	pH	Iodine mols/L. x 10^4
0	0.23125	0.2354	3.9	----
90	0.23125	0.2360	3.4	3.10
138	0.23062	0.2330	3.2	4.07
214	0.23019	0.2343	3.2	2.72
266	0.23240	0.2396	3.2	2.85
310	0.23196	0.2356	3.2	1.24
358	0.23240	0.2206	3.2	4.35
410	0.23076	0.2330	3.2	4.76
531	0.23142	0.2316	3.2	4.48
603	0.23142	0.2312	3.2	1.90
718	0.23103	0.2342	3.2	2.71
866	0.23129	0.2318	3.2	9.51
1126	0.23196	0.2368	3.2	2.04
1486	0.23137	0.2319	3.2	5.16
3122	0.23196	0.2312	3.2	1.90

It was concluded from these data that a limited supply of oxygen tends to prevent the progress of the decomposition.

In order to test further the effect of low oxygen

content upon the decomposition of ferrous iodide solutions, a solution corresponding in strength to that of the U.S.P. Syrup of Ferrous Iodide was prepared and stored in pycnometers which were promptly sealed with paraffin. The solution was prepared with card teeth and U.S.P. iodine and was 0.22598 molar with respect to ferrous iodide. Iodine appeared in a sample exposed to air in 10 minutes. Data follow:

Table 58.

Decomposition of Ferrous Iodide Solution-Sealed Pycnometers.

Hours	Precipitate	Appearance	K_m
0	None	Colorless	------
72	None	Pale yellow	------
168	None	Bubbles on surface-I_2	------
192	None	Bubbles on surface-I_2	8.80×10^{-6}
792	None	Bubbles on surface-I_2	2.59×10^{-6}

It was concluded from the above data that the reaction involving air occurred as long as oxygen was present in the water used in making the solution, but upon consumption of this quantity of air, the reaction involving oxygen ceased and in its stead, decomposition at a much slower rate, i.e., unimolecular first order decomposition of the type:

$$2\ H^+ + 2\ I^- \rightleftharpoons H_2 + I_2$$

represents the decomposition. This view is strengthened by a consideration of the quantity of air present. In 100 cc. of solution, (assuming the solubility of air in solution of ferrous iodide to be the same as in water), at 25° C., there are 0.003931 grams of oxygen (285). Since in the reaction

$$2\ HI + O \rightleftharpoons H_2O + I_2$$

it requires 16 grams of oxygen for each mol of iodine formed, there should be in this case,

$4.891 \times 10^{-4} \times 16 = 7.8256 \times 10^{-3}$ grams of oxygen. Since the pycnometers hold exactly 25 cc., there is actually contained in the solution only 0.003931/4 gram of oxygen and it is evident that considerably more iodine has been formed than can be accounted for upon the basis of the oxygen contained.

It was thought probable that the bubbles appearing in the solution might be bubbles of hydrogen gas from this secondary decomposition. Solutions of ferrous sulfate, stored in the same manner did not develop such bubbles, thus lending credence to this supposition.

D. The effect of light upon the rate of decomposition of solutions of ferrous iodide. It has long been known that the decomposition of iodide ion in the presence of

hydrogen ion is catalyzed by the action of light and Berthoud and Nicolet (293) have shown that all light from the visible spectrum is effective in increasing the rate of reaction.

In order to evaluate the effect of light upon the decomposition of ferrous iodide solutions, a sample of solution was prepared from card teeth and Reagent iodine, portions stored in direct sunlight behind a series of colored glass filters from the Corning Glass Works, and the progress of the reaction followed in the usual manner by titration of the iodine formed at frequent intervals.

The filters used and data regarding their spectral transmission follow:

Table 59.

Spectral Transmission of Light Filters.

Filter	Wave lengths Transmitted mu	80 % Transmission mu	Wave lengths cut off-mu
Noviol O	370 up	470	Below 370
Noviol C	470 up	505	Below 470
Heat Absorbing	320 up	370 - 620	Below 320
Heat Transmitting	No information available		
Yellow H.R. Red shade	570 up	700	Below 570
Yellow H.R. Yellow shade	485 up	600	Below 485

Table 59 - cont.

Spectral Transmission of Light Filters.

Filter	Wave lengths Transmitted mu	80 % Transmission mu	Wave lengths cut off-mu
Pale blue green	330-590	(70 %) 450	Below 330 Above 590
Red	590 up	610	Below 590
Blue purple ultra	100-500 (good) 500-670 (fair) 700 up (poor)	320	3% yellow Below 100
Red purple ultra	300-420 680 up	340-400	Below 300 440-680
Violet ultra	320-400	(35 %) 360	200-320 Above 400

Remembering that the spectrum scale is as follows:

300 mu-----Ultra violet
400 mu-----Violet
500 mu-----blue green
600 mu-----yellow orange
700 mu-----red,

it is evident that the following filters transmit heat:

Noviol O, Noviol C, Heat Transmitting, Yellow H.R. Red shade, Yellow H.R. Yellow shade, Red, Blue purple ultra, Red purple ultra. Similarly, heat rays are not transmitted by: Pale blue green or Violet ultra filters. Furthermore, the filters "cut out" from the lower end of the spectrum up as follows:

1. The data in Table 59 are obtained from U.S. Bureau of Standards Technologic Papers 148 and 119.

1. Blue purple ultra
2. Red purple ultra
3. Violet ultra
4. Heat absorbing
5. Pale blue green
6. Noviol O
7. Noviol C
8. Yellow H.R. Yellow
9. Yellow H.R. Red
10. Red

The following data upon the same filters were furnished by the manufacturers:

Filter	Lines present	Lines absent
Purple infra red transmitting	Infra red 1 u	Visible light
H.R. Ruby	Red	No yellow
Yellow H.R. Red shade	Yellow	No green
Yellow H.R. Yellow shade	Green	No blue green
Noviol Shade C	Blue green	No blue
Noviol Shade O	Violet	No ultra violet
Heat absorbing	Visible	Infra red
Ultra transmitting pale blue green	Ultra violet	No red
Ultra transmitting blue purple	Extreme red and blue	No yellow
Ultra transmitting red purple	Extreme red and violet	No green
Ultra transmitting violet	Ultra violet	No visible light

The data obtained from the solutions of ferrous iodide stored behind these light filters follow. It is noteworthy that in cases where a sample of solution was stored behind a filter transmitting only ultra violet light, the solution

was for all practical purposes in darkness since the type of glass used in the containers does not permit the passage of ultra violet light.

Table 60.

Decomposition of Solutions of Ferrous Iodide in Light.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
Noviol Shade O				
0	0	----	0.22690	-----
95	95	2.156	0.22475	10.2
263	168	6.278	0.22062	11.0
839	576	18.21	0.20869	9.6
Heat Transmitting				
0	0	----	0.22690	----
95	95	1.753	0.22505	8.4
263	168	5.117	0.22078	8.8
839	576	17.07	0.20983	9.6
Heat Absorbing				
0	0	----	0.22690	---
95	95	1.753	0.22505	8.4
263	168	5.224	0.22168	9.1
839	576	16.60	0.21030	9.2
Red purple ultra				
0	0	---	0.22690	---
95	95	1.836	0.22506	8.4

Table 60 - cont.

Decomposition of Solutions of Ferrous Iodide in Light.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	K_m x 10^5
Red purple ultra - cont.				
263	168	5.224	0.22168	9.1
839	576	16.23	0.21067	8.9
Blue purple ultra				
0	0	---	0.22690	---
95	95	1.895	0.22500	8.9
263	168	5.220	0.22168	8.8
839	576	16.90	0.21000	9.4
Violet ultra				
0	0	---	0.22690	---
95	95	1.895	0.22500	8.9
263	168	5.224	0.22168	8.8
839	576	16.47	0.21043	9.1
H.R. Yellow - Red Shade				
0	0	---	0.22690	---
95	95	1.919	0.22498	8.9
263	168	5.686	0.22121	10.1
839	576	17.78	0.20912	9.7
Red				
0	0	---	0.22690	---
95	95	1.990	0.22491	9.3

Table 60 - cont.

Decomposition of Solutions of Ferrous Iodide in Light.

Hours Total	Hours Segment	Iodine mols/L. x 10^5	Concentration mols/L. (a-x)	K_m x 10^5
Red - cont.				
263	168	5.804	0.22110	10.1
839	576	18.18	0.20872	10.0
Open Window - No glass - Control.				
0	0	---	0.22690	---
95	95	1.990	0.22491	9.3
263	168	6.041	0.22086	10.7
839	576	17.56	0.20934	9.3
H.R. Yellow - Yellow Shade				
0	0	---	0.22690	---
95	95	1.990	0.22491	9.3
263	168	5.804	0.22110	10.1
839	576	18.01	0.20889	9.9
Noviol C				
0	0	---	0.22690	---
95	95	2.014	0.22489	9.3
263	168	6.243	0.22066	11.2
839	576	19.55	0.20735	10.8
Pale blue green				
0	0	---	0.22690	---
95	95	2.014	0.22489	9.3

Table 60 - cont.

Decomposition of Solutions of Ferrous Iodide in Light.

Hours Total	Hours Segment	Iodine mols/L. x 10^3	Concentration mols/L. (a-x)	$K_m \times 10^5$
Pale blue green - cont.				
263	168	5.591	0.22131	9.6
839	576	16.61	0.21029	8.9

If we average the specific reaction rates in each case from the data as obtained in Table 60, we have the following:

Table 61.

Specific Reaction Rates of Solutions of Ferrous Iodide Exposed to Selective Spectral Bands.

Filter	$K_m \times 10^5$
Noviol O	10.3
Heat Transmitting	8.9
Heat Absorbing	8.9
Red Purple Ultra	8.8
Violet Ultra	9.0
H.R. Yellow (yellow shade)	9.4
H.R Yellow (red shade)	9.6

Table 61 - cont.

Specific Reaction Rates of Solutions of Ferrous Iodide Exposed to Selective Spectral Bands.

Filter	$K_m \times 10^5$
Red	9.8
Noviol C	10.4
Pale blue green	9.3
Control	9.8

From the above data it was concluded that since no significant difference was shown by the specific reaction rate under the influence of selective spectral bands, the rate of reaction is probably catalyzed by all parts of the visible spectrum. This conclusion is in accord with experimental results obtained by other investigators upon the photochemical oxidation of iodide ion (294).

In order to test the action of light from the ultra violet region of the spectrum upon the rate of decomposition of solutions of ferrous iodide, a solution assaying 0.2332 mols/L. of ferrous iodide was prepared from card teeth and Reagent iodine, divided into four 50 cc. portions and stored as follows: (a) in a quartz flask in open sunlight; (b) in a pyrex flask in open sunlight; (c) in a quartz flask behind the ultra violet transmitting filter; and

(d) in a pyrex flask behind the ultra violet transmitting filter. Flasks were so chosen as to allow approximately the same surface exposure in every case and contained an excess of air. The solutions were analyzed for iodine at the end of one, two and three weeks but no difference in the quantity of iodine contained could be detected in any case. It was concluded that the action of ultra violet light is without effect upon the decomposition of solutions of ferrous iodide.

The Appearance of Permanent Dark Coloration other than that due to Iodine. It has been noted by various authorities that syrups containing ferrous iodide turn dark in color on long standing. This phenomenon has led to much confusion in the literature, some authorities assuming it to be due to free iodine and others regarding it as a separate form of decomposition.

Phillips (248) believed this color to be due to the formation of a "per-salt" of iron; Fruckhinger (249) found that the evaporation of solutions of ferrous iodide containing sucrose gave a black residue of humic substance; Salzer (255) ascribed the coloration to a mixture of iodized starch and ferrous oxide; Haussmann (257) regarded the color as due to the decomposition of levulose resulting from sucrose inversion; and Arny and co-workers (127, 128,

129) stated the discoloration to be due to caramelization occasioned by the presence of hypophosphorous acid. Obviously, since aqueous solutions of ferrous iodide do not show this phenomenon, the coloration must be due either to sucrose or tis inversion products, hypophosphorous acid, iodine or to ferric hydroxide, or to substances formed by interaction of these compounds.

In order to determine the effect exerted by various substances present in Syrup of Ferrous Iodide upon sucrose alone, samples of simple syrup were prepared and the substance added in various proportions. Observations were made at intervals. Hypophosphorous acid, ferrous ion as ferrous sulfate, phosphoric acid, iodine and potassium hypophosphite were the substances added. Samples marked "(C)" in Table 62, contain approximately the same amount of that ingredient as is specified in the U.S.P. X formula for Syrup of Ferrous Iodide.

Table 62.

The Effect of Various Chemicals upon Sucrose.

Cc. or Gm. of chemical per liter.	65 days	291 days
5.5 H_3PO_2 (C)	clear-colorless	faint tan color
10.8 H_3PO_2	clear-colorless	dark tan color
14.4 H_3PO_2	clear-colorless	brown color

Table 62 - cont.

The Effect of Various Chemicals upon Sucrose.

Cc. or Gm. of chemical per liter.		65 days	291 days
20.0	H_3PO_2	clear-colorless	very brown color
36.0	$FeSO_4$	clear-colorless	clear-colorless
70.5	$FeSO_4$ (C)	clear-colorless	distinct tan color
100.8	$FeSO_4$	clear-colorless	pale brown color
144.0	$FeSO_4$	clear-colorless	pale brown color
36.0	H_3PO_4	clear-colorless	pale tan color
72.0	H_3PO_4	clear-colorless	light brown color
102.0	H_3PO_4	clear-colorless	brown color
144.0	H_3PO_4	clear-colorless	brown color
.00455	I_2	clear-colorless	clear-colorless
.00910	I_2	silver tinge	clear-colorless
.01365	I_2	faint green-black	clear-colorless
.01820	I_2	green-black	clear-colorless
7.2	KH_2PO_2	clear-colorless	clear-colorless
Control		clear-colorless	clear-colorless

It was concluded from these data, that hypophosphorous and phosphoric acids tend to cause a brown coloration to appear in sucrose solutions even though iron or iodine are absent. This conclusion is in accord with that of Franklin (301). Ferrous iron alone also has this tendency,

possibly due to the formation of peptized ferric hydroxide in the syrup. The tendency is, however, much more marked in the case of the acids. Iodine solutions, on the other hand, gradually pass through several stages of coloration in the presence of sucrose and are eventually decolorized completely without producing any final difference in the color of the sucrose solutions.

A sample of a solution containing diluted hypophosphorous acid and ferrous sulfate was prepared and stored at the same time as the above samples. At the end of 8 months, it contained a white crystalline precipitate in the bottom of the bottle, but the solution remained quite colorless.

Although the data in Table 62 indicate that dark colorations are formed in simple syrup by the presence of hypophosphorous or phosphoric acids and by ferrous iron, it was thought advisable to determine whether syrups prepared with ferrous iodide would darken in the absence of acid. For this purpose, samples of U.S.P. Syrup of Ferrous Iodide with acid omitted, were stored in the electric oven at 50° C., in direct sunlight and in darkness at room temperature in containers containing excess air and in tightly-stoppered, completely filled bottles. The procedure was followed simultaneously with a syrup prepared from card teeth and one prepared from Reagent

iron and repeated with a U.S.P. sample for control purposes. In one month, all oven samples had darkened; in three months all samples stored in direct sunlight were black; and in 6 months, samples stored in darkness had deteriorated similarly. The black appearance of the syrups was partially due to the presence of a dark colored precipitate although the filtrates were very dark in color. Samples upon analysis, showed no loss of total iodide as would be expected if the iodine had entered into organic combination. No free iodine was contained in any of the samples. Moreover, small quantities of iodine added to the filtrates rapidly disappear. A microscopic examination of the precipitates showed them to be amorphous particles, similar in every respect to ferric hydroxide. It was concluded that although the presence of hypophosphorous acid may hasten the appearance of black coloration, it is not, as commonly supposed, essential that the acid be present for the decomposition to occur. Similarly, free iodine cannot be responsible, since it cannot exist in the presence of hypophosphorous acid. Heat and air accelerate the change. This conclusion agrees with that of Berg and Becker (126).

A sample of U.S.P. Syrup of Hydriodic Acid, which also contains hypophosphorous acid, was next subjected, simultaneously with a control sample of U.S.P. Syrup of

Ferrous Iodide, to the conditions outlined above. After one months exposure in the oven, the syrup containing iron was black; that containing hydriodic acid was dark brown, Both samples contained a black precipitate. It was concluded that the coloration in Syrup of Ferrous Iodide is probably composed of two factors, i.e., a brown coloration produced by the formation of peptized ferric hydroxide and a black precipitate partially peptized which is due to the action of the acids on the sugars.

Sucrose, upon inversion, furnishes equimolecular quantities of levulose (d-fructose) and dextrose and Krantz (130) has shown that the sucrose contained in Syrup of Ferrous Iodide is 96.2 % inverted at the end of 20 days. In order to determine which of the sugars was responsible for the discoloration, a syrup containing 700 Gm./L. of C.P. dextrose was prepared and stored in the oven at 50° C. and in sunlight in tightly-stoppered, completely filled bottles and in an excess of air. A U.S.P. sample was stored in the same way for comparative purposes. At the end of one month, samples from C.P. dextrose showed no change; the U.S.P. samples stored in the oven were black and the samples stored in sunlight were brown. At the end of two months, the dextrose samples stored in the oven in excess air were pale tan while that in a completely filled bottle showed no change. No further

changes were noted in samples stored in sunlight. It was concluded that either levulose or sucrose, probably the former, is responsible for the discoloration or precipitation, although some slight discoloration may result from peptized ferric hydroxide as in the case of the dextrose sample stored in the presence of air.

Two compounds, lead fructosate, $C_6H_{12}O_6 \cdot 2\ Pb(OH)_2$, and $C_6H_{12}O_6 \cdot 2\ PbCl_2$ are known (295, 296). The former is dark yellow in color; the latter is dark brown. Both are precipitated by alcohol. The compound $2\ C_6H_{12}O_6 \cdot 3\ Fe_2O_3\ 3\ H_2O$ has also been described (297) as an orange-red amorphous precipitate insoluble in alcohol. In order to determine whether a similar compound might be formed in the case of ferrous iodide, the black filtrate from deteriorated sucrose solutions was poured into a large excess of 95 % alcohol. The filtrate was partially decolorized and upon standing, an orange-red amorphous precipitate appeared. It was concluded that some indication exists that a compound between ferrous iodide and levulose may be formed in the syrup, although levulose is capable of furnishing the dark coloration in the absence of iron, as shown by the darkening of Syrup of Hydriodic Acid.

6. The Evaluation of Preservatives.

The mass of conflicting data regarding the preservation of Syrup of Ferrous Iodide has been briefly summarized (p 43), and, in general, it may be said that the suggested methods of preservation are the result of empirical studies and a trial and error method of research. Obviously, the value of any preservative or stabilizer is dependent, a fact not previously recognized, upon the three factors (a) the effect of the stabilizer upon the rate of iodine formation, (b) reaction of the stabilizer with iodine, and (c) the formation of undesirable compounds with other ingredients present. It is also evident, that these factors may vary directly or inversely with each other or may be affected differently by heat and light and it is to this multiple character of preservative action that much of the controversial data may be attributed.

It has been shown in this investigation that the absence of oxygen as well as a condition of optimum viscosity decreases the rate of iodine formation; the action of light has been shown to play no appreciable part in this phase of decomposition; and the effects of impurities and temperature have been noted. With this information at hand, it was possible to evaluate the action of preservatives upon a more logical basis than any formerly

used.

The methods of preservation and stabilizers previously suggested may be conveniently divided into three groups, the addition of carbohydrates, the addition of chemicals, and changes in the technique of manufacture, many of these suggestions being impractical either from the standpoint of ease of manipulation, pharmaceutical elegance, or therapeutic contra-indication. From the suggestions at hand, the following were chosen as being of sufficient importance to warrant further study: The addition of sucrose (10, 17), lactose (15), honey (15), glucose (68, 76, 85, 88, 98, 100, 102), glycerin (33, 54, 59, 63, 69, 70, 82, 102, 130), sodium thiosulfate (39, 40, 52), tartaric acid (41, 123), citric acid (77, 79, 86, 87, 113, 114, 116, 123, 126), hypophosphorous acid (50, 62, 72, 74, 85, 90, 91, 93, 96, 99), alcohol (60, 115), the effect of light (36, 98, 103, 115, 127), and storage in a cool place (77). The action of tragacanth has already been considered in the data on the effect of viscosity; and decomposition data have shown the reaction to progress at precisely the same rate for concentrated solutions, thus rendering valueless the highly regarded suggestion (38) that stability is achieved by concentrating the solution.

In accordance with the above discussion, the

preservatives chosen for further study were investigated regarding their action on free iodine, hypophosphorous acid and sodium thiosulfate being omitted since the reaction in this case is practically instantaneous. Time did not permit, however, of a study of the action of each of these substances under all conditions of temperature and light, the work being confined to experimentation in darkness at 30° C., thus approaching the approximate conditions of storage in practice[1]. Solutions were first prepared approximately 0.01 molar with respect to iodine and 2.484 molar with respect to preservative, the latter figure representing the concentration of sucrose in the U.S.P. Syrup of Ferrous Iodide, stored in glass-stoppered bottles containing excess air and the progress of the reaction followed by titrating the free iodine with approximately 0.01 N sodium thiosulfate solution. The data as obtained in these experiments follow in Table 63.

Table 63.

The Action of Certain Stabilizers upon Iodine Alone.

Substance added	Hours	Iodine mols/L.
Control (I_2 and KI in H_2O)	0	0.009781

1. These conditions were chosen as representing those most commonly found in the storage of prescription ingredient in pharmacies, as well as offering data directly comparable/s with previous parts of this investigation.

Table 63 - cont.

The Action of Certain Stabilizers upon Iodine Alone.

Substance added	Hours	Iodine mols/L.
Control - cont.	552	0.009781
	1128	0.009725
	1437	0.009756
Lactose 170 Gm./L.	0	0.008936
	552	0.008825
	1104	0.008600
	1413	0.008284
Glycerin	0	0.010097
	552	0.009737
	1133	0.010320
	1421	0.010064
Sucrose	0	0.009967
	552	0.009263
	1124	0.007859
	1440	0.007188
Dextrose	0	0.009834
	552	0.006574
	1124	0.005828
	1440	0.005409
Honey	0	0.009769
	552	0.004489
	1106	0.003328

Table 63 - cont.

The Action of Certain Stabilizers upon Iodine Alone.

Substance added	Hours	Iodine mols/L.
Honey - cont.	1394	0.003355
Alcohol	0	0.010029
	552	0.010080
	1107	0.010210
	1395	0.010406
Citric Acid	0	0.009961
	552	0.009595
	1132	0.009180
	1420	0.008935
Tartaric Acid	0	0.009999
	552	0.010420
	1130	0.010635
	1418	0.011125

From the data in Table 63, it was concluded that sucrose, dextrose, lactose, honey and, to a lesser degree, citric acid, exert a slow chemical action upon iodine in aqueous media in the presence of iodide ion. On the other hand, glycerin, tartaric acid, alcohol and tragacanth show no such action under the conditions of the experiment.

In order to evaluate the action of sucrose, honey and

dextrose (citric acid was not used because of its slow action and lactose was discarded on pharmaceutical grounds because of lack of sweetness and solubility), solutions of ferrous iodide containing these substances in the proportion of 2.484 mols per liter, calculating honey as dextrose, were treated with sufficient iodine to render them approximately 0.01 molar, stored in the thermostat at 30° C. and the rate of iodine disappearance noted. Thus this experiment measured the action of the preservative in the presence of ferrous iodide itself. It must be considered, of course, that the iodine present at any time of analysis represents the total of the iodine liberated by the solution during decomposition in that time, and the iodine remaining unconverted in the preparation. The iodine liberated during any time can readily be calculated from the equation:

$$K = \frac{2.303}{t} \log \frac{a}{(a-x)}$$

providing the value of K at the viscosity of the preparation is known. Thus in the case of the dextrose sample in Table 64 which has a relative viscosity of 5.8 at 30° C. compared to water at the same temperature, reference to the graph (p 177) shows the value of K to be approximately 1.05×10^{-5} and substituting to find the amount of iodine liberated in 341 hours,

$$1.05 \times 10^{-5} = \frac{2.303}{341} \log \frac{.22700}{(a-x)}$$

or (a-x) equals 0.22620 and therefore, the iodine liberated during this period is 8.0×10^{-4} mols per liter. The data in Table 64 show the molarity of the solution in iodine and the amount of iodine converted, calculated in each case according to the above illustration.

Table 64.

The Effect of Ferrous Ion upon the Rate of Iodine Conversion by Sucrose, Honey and Dextrose.

Hours	Iodine present mols/L.	Iodine formed mols/L.	Iodine converted mols/L.	Rate decomp. (p 177)	Viscosity Relative
Sucrose-Iodine-Ferrous Iodide 30° C.					
0	1.1134	----	----	0.85×10^{-5}	121.8
120	1.0601	.00031	.0536	0.85×10^{-5}	121.8
404	0.9772	.00081	.1370	0.85×10^{-5}	121.8
720	0.9688	.00144	.1460	0.85×10^{-5}	121.8
Sucrose-Iodine-Ferrous Iodide 50° C.					
0	1.1632	----	----	6.00×10^{-5}	89.3
48	0.4750	.00069	.6889	6.00×10^{-5}	89.3
112	0.0000	.00159	1.1648	6.00×10^{-5}	89.3
Honey-Iodine-Ferrous Iodide 30° C.					
0	0.9654	0.0000	0.0000	1.60×10^{-5}	3.63
120	0.8055	.00045	.1604	1.60×10^{-5}	3.63
404	0.7344	.00150	.2325	1.60×10^{-5}	3.63
720	0.7189	.00267	.2492	1.60×10^{-5}	3.63

Table 64 - cont.

The Effect of Ferrous Ion upon the Rate of Iodine Conversion by Sucrose, Honey and Dextrose.

Hours	Iodine present mols/L.	Iodine formed mols/L.	Iodine converted mols/L.	Rate decomp. (p 177)	Viscosity Relative
Honey-Iodine-Ferrous Iodide 50° C.					
0	0.9751	----	-----	9.00×10^{-5}	1.40
48	0.3151	0.00102	0.6610	9.00×10^{-5}	1.40
120	0.1054	0.00251	0.8722	9.00×10^{-5}	1.40
216	0.0296	0.01449	0.9600	9.00×10^{-5}	1.40
Dextrose-Iodine-Ferrous Iodide 30° C.					
0	1.1002	----	----	1.05×10^{-5}	5.80
341	1.3085	0.00081	-0.2072	1.05×10^{-5}	5.80
893	1.7800	0.00212	-0.6779	1.05×10^{-5}	5.80
Dextrose-Iodine-Ferrous Iodide 50° C.					
0	0.8766	----	----	6.00×10^{-5}	3.65
48	0.8529	0.00075	0.0245	6.00×10^{-5}	3.65
96	0.8671	0.00130	0.0108	6.00×10^{-5}	3.65

The concentrations from which calculations were made in Table 64 were as follows: dextrose samples 0.22700 mols/L., honey samples 0.23257 mols/L., and sucrose 0.23531 mols/L. with respect to ferrous iodide. The negative values prefixing the data for the dextrose sample at 30° C. indicate that that quantity of iodine was formed

in excess of the calculated value.

From the data in Table 64, it was concluded that heat tends to accelerate the iodine carbohydrate reaction to a much greater extent than the decomposition reaction; honey is apparently the most satisfactory preservative at 30° C, while sucrose is superior at 50° C.; and, the rate of decomposition of the sample containing dextrose is much more rapid than would be expected. In addition, a comparison of the data in Table 63 with that in Table 64 indicates that the disappearance of iodine is much more rapid in the presence of ferrous iodide than in aqueous solution.

Since the data in Table 64 would indicate that solutions of ferrous iodide containing 2.484 mols/L. of honey or sucrose would be perfectly stable at 30° C. in darkness while solutions with dextrose would deteriorate, a series of experiments designed to test this point as well as to verify the conclusions so far reached as regards preservation were performed. Samples of solutions of ferrous iodide were prepared and stored in darkness at 30° C. in the thermostat, each solution containing 2.484 mols/L. of a preservative and being stored in the presence of excess air. A detailed consideration of each sample is contained in the following pages.

A sample was prepared exactly according to the U.S.P. X directions with, however, the hypophosphorous acid omitted. The pH was determined with meta-cresol purple and La Motte yellow to be 2.4. The total iodide content was 0.2239 mols/L. No iodine in the free state was contained in the finished preparation. The rate of reaction was followed in the usual manner and values of K_m, the first order reaction rate are calculated for comparative purposes. Data are shown in Table 65.

Table 65.

Sucrose as a Preservative.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^5	K_m x 10^6
0	0	2.4	----	------
124½	124½	2.4	4.076	3.33
291	166½	2.4	----	------
671	380	2.4	----	------
1011	340	2.4	----	------
1563	552	2.4	----	------
3003	1440	2.4	----	------

As indicated in Table 65, a trace of iodine appeared in the preparation at the end of 125 hours, but disappeared again and did not return. It would seem, therefore, that at temperatures of 30° C. and above, sucrose preserves the

preparation perfectly as far as iodine liberation is concerned, since the sucrose-iodine reaction is more rapid than is the auto-oxidation. It was observed, however, that at frequent intervals, slight iodine tinges appeared at the surface of the syrup. Upon shaking the preparation, however, no test for iodine could be obtained. It is probable, therefore, that the 30° C. temperature is very close to the limiting temperature for preservation.

These data are of interest in that they offer an explanation of the fact often reported in the literature by investigators who claimed that a U.S.P. Syrup of Ferrous Iodide made without hypophosphorous acid did not spoil, only to have their claims disputed by others who probably worked at lower temperatures.

A sample was next prepared containing 2.484 mols per liter of dextrose. The pH of this preparation was pH 2.5, only 680 cc. of water being used to make a liter of finished product. The data are shown in Table 66.

Table 66.

The Preservative Action of Dextrose.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^6	K_m x 10^6 (Segment)	K_m x 10^6 (Total)
0	0	2.5	----	----	----
243½	243½	2.6	0.408	7.09	7.09

Table 66 - cont.

The Preservative Action of Dextrose.

Hours Total	Hours Segment	pH	Iodine mols/l. x 10^3	$K_m \times 10^6$ (Segment)	$K_m \times 10^6$ (Total)
622½	379	2.8	1.100	8.02	7.66
964	341½	3.1	1.309	2.56	5.85
1516	552	3.2	1.780	2.67	5.01
2956	1440	3.2	2.054	6.25	5.69

As would be expected from the data in Table 63, and as indicated in Table 66, dextrose shows some preservative action. The values of K_m, although showing some fluctuation in the earlier stages of the reaction, return to the original rate after the passage of approximately 3000 hours and furnish a fairly reliable value for K_m when calculated upon the total hour basis. The data shown above account in a measure for the results obtained by investigators who found dextrose to be advantageous. The variation in pH in this preparation, is of interest in that it rises steadily from the time of manufacture until it reaches the point at which secondary equilibrium occurs in aqueous solutions. Although these data are not in accord with those shown in Table 64 for dextrose, they may be considered more reliable since the conditions of the experiment more nearly approach actual practical conditions.

A sample was next prepared exactly according to the U.S.P. directions with hypophosphorous acid omitted, but using Reagent iron rather than card teeth as the form of iron. It was stored as in the previous instances. The pH of this solution was pH 4.2. It assayed 0.2219 mols/L. of total iodide. Data follow:

Table 67.

The Effect of Reagent Iron upon the Preservative Action of Sucrose.

Hours Total	Hours Segment	pH	Iodine mols/L.	K_m (Segment)	K_m (Total)
0	0	4.2	----	-----	----
117	117	4.1	----	-----	----
496	379	4.8	----	-----	----
832	336	4.9	----	-----	----
1384	552	4.2	----	-----	----
2824	1440	4.1	----	-----	----

As indicated in Table 67, results are analogous to Table 65. A surface tinge was also noted in this sample but the quantity was too slight for analysis. The puzzling behavior of the pH values are possibly due to the difficulty in determinations of pH in the presence of sucrose. It was concluded that syrups made either with Reagent iron or card teeth and sucrose, keep well at 30° C.

in darkness, even though excess air is present.

A sample containing 0.47 mols/L. of lactose, the maximum solubility, was next prepared and stored as in the preceding cases. The solution was 0.2273 molar with respect to ferrous iodide and the pH was 2.7. Data follow:

Table 68.

The Preservative Action of Lactose.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^3	$K_m \times 10^5$ (Segment)	$K_m \times 10^5$ (Total)
0	0	2.7	----	-----	-----
191	191	3.3	1.127	2.55	2.55
533	342	3.5	1.753	0.84	1.02
1085	552	3.8	4.212	1.98	1.72
2525	1440	4.1	9.619	1.72	1.71

As indicated in Table 68, the concentration of lactose herein represented effects some preservative action, being of about the same power as the use of pure iron in a simple aqueous solution. The puzzling behavior of the pH is not accounted for in this sample. It is probable that the inferior power of lactose as a preservative is due not only to the low concentration but also to the low relative viscosity produced in comparison with the other sugars. Precipitation was noticed in the sample at the end of

about 1000 hours, although it later disappeared.

A sample was next prepared using honey as the preservative. The molecular weight of this substance being indeterminate, 500 Gm./L., corresponding to the approximate weight of dextrose used in Table 66, was used. The pH was 2.6 and analysis showed a total iodide content of 0.2278 mols/L. of ferrous iodide. Data follow:

Table 69.

The Preservative Action of Honey.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^4	K_m (Segment)	K_m (Total)
0	0	2.6	----	-----	-----
168	168	2.8	----	-----	-----
510	342	2.6	----	-----	-----
1062	552	2.6	----	-----	-----
2520	1440	2.6	4.792	-----	-----

As indicated in Table 69, honey in the quantity used acts as a very efficient preservative for some period of time. At the end of 2520 hours, however, iodine appeared in the preparation. No calculation of specific reaction rates was made, however, since it appears probable that this iodine content represents not so much the accumulation of a small amount of iodine but rather the sudden liberation of

this element at the expiration of the inhibiting substance in honey. It would seem probable that the preservative action of honey after the appearance of iodine would approach that of dextrose alone.

A sample was next prepared using glycerin in the proportion of 2.484 mols/L., the preparation being 0.2287 molar with respect to ferrous iodide. The pH was 3.5 to La Motte yellow and 3.9 to bromphenol blue. Data follow:

Table 70.

The Preservative Action of Glycerin.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^3	K_m x 10^5 (Segment)	K_m x 10^5 (Total)
0	0	3.5	----	----	----
145½	145½	3.5	0.544	1.50	1.50
486	340½	3.4	1.223	0.93	1.04
1038	552	3.4	3.900	2.14	1.66
2478	1440	3.4	5.306	0.44	0.95

As indicated in Table 70, the rate of decomposition as evaluated in terms of the segment specific reaction rate tends to slow considerably as time goes on. In other words, the percentage decomposition per unit of time is decreasing. The total specific reaction rate, however, indicates approximately a threefold decrease in the rate of

decomposition over that of an aqueous solution alone.

Although previous experiments had shown that citric acid and tartaric acid possess little preservative value, a sample was prepared containing 2.484 mols/L. of citric acid and being 0.2193 molar with respect to ferrous iodide. The pH was 0.4 to acid cresol red. Data follow:

Table 71.

The Preservative Action of Citric Acid.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^3	$K_m \times 10^5$ (Segment)	$K_m \times 10^5$ (Total)
0	0	0.4	---	-----	----
166	166	0.4	0.815	2.21	2.21
598	432	0.4	2.445	1.74	1.87
958	360	0.4	3.701	1.62	1.78
1335	377	0.4	4.789	1.25	1.63
2775	1440	0.4	10.61	1.93	1.79

This preparation showed no trace of precipitation at any time. The values of the specific reaction rate as shown in Table 71, are in fair agreement and the rate of decomposition is approximately half that of the standard solution alone.

A sample was next prepared containing 2.484 mols/L.

of tartaric acid and was 0.2244 molar with respect to ferrous iodide, although analysis was very difficult due to darkening of the solution during titration. The pH was 0.4 to acid cresol red. Data follow:

Table 72.

The Preservative Action of Tartaric Acid.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^3	K_m x 10^5 (Segment)	K_m x 10^5 (Total)
0	0	0.4	----	-----	-----
163	163	0.4	0.815	2.19	2.19
595	432	0.4	2.351	1.66	1.81
955	360	0.4	5.503	3.90	2.60
1332	377	0.4	7.166	2.02	2.43
2394	1062	0.4	15.74	3.80	3.04

As indicated in Table 72, the hydrogen ion concentration is similar to that produced by the addition of 2.484 mols of citric acid. The rate of oxidation in this case, fluctuates more markedly than is the case with the citric acid preparation and it is apparent from the data that citric acid is a more satisfactory preservative than is tartaric acid.

A sample was next prepared containing alcohol as the preservative in the proportion of 2.484 mols/L. and the

solution was 0.2266 molar with respect to ferrous iodide. The pH was 3.2 to La Motte yellow. Data follow:

Table 73.

The Preservative Action of Alcohol.

Hours Total	Hours Segment	pH	Iodine mols/L. x 10^3	K_m x 10^5 (Segment)	K_m x 10^5 (Total)
0	0	3.2	----	-----	-----
166	166	3.1	0.652	1.60	1.60
598	432	3.1	2.975	2.45	2.21
934	336	3.1	4.755	2.30	2.24
2374	1440	3.1	9.242	1.44	1.75

As shown by the data in Table 73, alcohol exerts some small preservative effect, although the values obtained are not in good agreement.

Viscosity data as obtained at 30° C. on the samples considered in Tables 65 to 73 inclusive, follow in Table 74. "Zeta", the coefficient of viscosity, is calculated from the formula:

$$\text{zeta} = \frac{(\text{time} \times \text{density})_{\text{unknown}}}{(\text{time} \times \text{density})_{\text{water}}}$$

The absolute viscosity in terms of the poise is obtained by multiplying the coefficient of viscosity by the absolute viscosity of water. The time listed in Table 74, refers

to the time required for the solution to pass through the capillary of the viscosimeter tube. It is understood that the pH of alcoholic solutions determined colorimetrically is only an apparent value, since alcohol affects the dissociation constant and consequently the shade of color of the indicator.

Table 74.

The Viscosity of Solutions of Various Preservatives.

Solution	Time	zeta	Absolute	pH
Water	1' 30 2/5"	1.000	0.00895 poise	5.7
Ferrous Iodide	1' 30 2/5"	1.072	0.00959 poise	3.2
Sucrose (Reagent iron)	2 hours 13' 45"	121.83	1.0903 poise	4.2
Sucrose (Card teeth)	2 hours 13' 45"	121.83	1.0903 poise	2.4
Dextrose	7' 3 4/5"	5.805	0.05195 poise	2.5
Lactose	2' 14 1/5"	1.675	0.01495 poise	2.8
Honey	4' 27 4/5"	3.627	0.03246 poise	2.6
Glycerin	2' 29"	1.844	0.01650 poise	3.5
Alcohol	2' 24"	1.733	0.01552 poise	3.2
Tartaric acid	3' 41 2/5"	3.012	0.02696 poise	0.4
Citric acid	4' 9"	3.415	0.03056 poise	0.4

As indicated in Table 74, the viscosity of a solution containing alcohol is greater than that of an aqueous solution alone. This unusual behavior was also found to

apply to alcohol-water mixtures in the absence of ferrous iodide.

Canals and Baumelow (300) found the viscosity of Syrup of Ferrous Iodide to be 1.40 poises at 15° C., as compared with that of 1.09 poises found at 30° C. in this investigation.

Table 75 shows the rate of decomposition as obtained from viscosity data alone in comparison with the averages of the decomposition rates obtained from the data in Tables 65 to 73 inclusive. These values are based on the assumption that the effect of tragacanth is due solely to the viscosity imparted to the solution and that this effect will hold for other substances.

Table 75.

The Effect of Preservatives on the Rate of Decomposition.

Sample	Rate of decomp. from viscosity data (p 177).	Actual rate of decomp.
Sucrose (card teeth)	8.5×10^{-6}	--------
Dextrose	1.05×10^{-5}	5.36×10^{-6}
Sucrose (Reagent iron)	8.5×10^{-6}	--------
Lactose	2.5×10^{-5}	1.77×10^{-5}
Honey	1.56×10^{-5}	--------
Glycerin	2.10×10^{-5}	1.25×10^{-5}

Table 75 - cont.

The Effect of Preservatives on the Rate of Decomposition.

Sample	Rate of decomp. from viscosity data (p 177).	Actual rate of decomp.
Citric acid	1.50×10^{-5}	1.75×10^{-5}
Tartaric acid	1.65×10^{-5}	2.71×10^{-5}
Alcohol	2.07×10^{-5}	1.95×10^{-5}

As indicated in Table 75, sucrose and honey show strong preservative action; dextrose, lactose and glycerin possess only feeble preservative properties; and citric and tartaric acids accelerate the rate of decomposition. Alcohol is apparently without appreciable effect. The acceleration shown by the acids may be attributed to increased hydrogen ion concentration, for it is well known that increasing acidity hastens the decomposition of iodide ion (298).

The Action of Preservatives under Practical Conditions. In order to verify the results thus far obtained as to the action of preservatives, as well as to gain further information as to the action of these stabilizers under various conditions, a series of preparations was stored under conditions of darkness at room temperature, diffused light at room temperature, sunlight and in the refrigerator in darkness. Each sample was stored under conditions of

excess air and in completely filled, tightly-stoppered bottles. The following samples were used:

1. Solution of ferrous iodide containing 500 cc. of honey per liter.

2. Solution of ferrous iodide containing 250 cc. of honey per liter.

3. Solution of ferrous iodide containing 425 grams of sucrose and 425 cc. of honey per liter.

4. Solution of ferrous iodide containing 800 grams of sucrose and 50 grams of honey per liter.

5. Solution of ferrous iodide containing 800 grams of dextrose and 10 % of ferrous iodide per liter.

6. U.S.P. Syrup of Ferrous Iodide without hypophosphorous acid and prepared by the use of card teeth.

7. U.S.P. Syrup of Ferrous Iodide prepared from card teeth.

8. U.S.P. Syrup of Ferrous Iodide containing sodium thiosulfate but no hypophosphorous acid.

9. U.S.P. Syrup of Ferrous Iodide containing no hypophosphorous acid but 10 % in strength with respect to ferrous iodide.

10. U.S.P. Syrup of Ferrous Iodide without hypophosphorous acid but which contained 0.2949 Gm./L. of NaOH. The pH was about 5.5 and the preparation very deep green in color.

11. U.S.P. Syrup of Ferrous Iodide without hypophosphorous acid and with the addition of 0.6908 Gm./L. of NaOH.

12. U.S.P. Syrup of Ferrous Iodide without hypophosphorous acid and containing 0.1975 Gm./L. of NaOH. The pH was 5.4.

13. U.S.P. Syrup of Ferrous Iodide prepared by the use of Reagent iron.

14. U.S.P. Syrup of Ferrous Iodide prepared without hypophosphorous acid but using Reagent iron.

15. U.S.P. Syrup of Ferrous Iodide prepared without hypophosphorous acid but containing 5 grams per liter of hydroquinone.

16. A sample of solution of ferrous iodide containing 80 % glycerin and no hypophosphorous acid.

The data obtained from an examination of these samples follow:

Table 76.

Appearance of Samples Stored in the Presence of Air at the End of 4 Months.

Sample	Dark	Diffused	Sun	Refrig.
U.S.P. control	pale brown no I_2-scum	light brown no I_2-crystal	Black no I_2	Tan trace I_2
U.S.P. Reagent iron	pale tan no I_2	light brown no I_2	Black no I_2	pale no I_2
U.S.P. less H_3PO_2	brown-I_2	brown-I_2	Black no I_2	I_2
U.S.P. less H_3PO_2 (Reag. iron)	good color no I_2	perfect	Black no I_2	I_2
U.S.P. 10 %	brown-I_2	brown- I_2	Black trace I_2	I_2
U.S.P. 0.1975 NaOH	good color no I_2	perfect	murky no I_2	I_2
U.S.P. 0.2949 NaOH	yellow no I_2	trace I_2	Black no I_2	I_2
U.S.P. 0.6908 NaOH	pale brown no I_2	yellow no I_2	Black no I_2	I_2
U.S.P. $Na_2S_2O_3$	Free S trace I_2	Free S trace I_2	Black no I_2	yellow no I_2
Dextrose 10 % FeI_2	brown free I_2	brown free I_2	Brown I_2	solid I_2
Honey 250 cc./L.	brown- I_2	brown-I_2	Black no I_2	I_2
Honey 500 cc./L.	brown- I_2	brown-I_2	Black no I_2	I_2
Honey 50; sucrose 800.	good color no I_2	trace I_2	Black No I_2	I_2

Table 76 - cont.

Appearance of Samples Stored in the Presence of Air at the End of 4 months.

Sample	Dark	Diffused	Sun	Refrig.
Honey 425; sucrose 425	scum no I_2	scum no I_2	Black no I_2	I_2
Glycerin 80 %	I_2	I_2	perfect	I_2
Hydroquinone	perfect	perfect	perfect	I_2

Table 77.

Appearance of Samples Stored in Completely Filled Bottles.

4 Months Exposure.

Sample	Dark	Diffused	Sun	Refrig.
U.S.P. control	pale brown no I_2	light brown no I_2	broken	perfect
U.S.P. Reagent iron	pale tan no I_2	light brown no I_2	broken	perfect
U.S.P. less H_3PO_2	perfect no I_2	perfect no I_2	broken	trace I_2
U.S.P. less H_3PO_2 (Reag. iron)	perfect	perfect	broken	trace I_2
U.S.P. 10 %	trace I_2	perfect	broken	I_2
U.S.P. 0.1975 NaOH	pale green no I_2	pale green no I_2	perfect	green in bottom
U.S.P. 0.3949 NaOH	green no I_2	green no I_2	perfect	dark green-I_2
U.S.P. 0.6908 NaOH	dark green no I_2	dark green no I_2	perfect	dark green-I_2

Table 77 - cont.

Appearance of Samples Stored in Completely Filled Bottles.

4 Months Exposure.

Sample	Dark	Diffused	Sun	Refrig.
U.S.P. $Na_2S_2O_3$	pale green no I_2	cloudy no I_2	broken	cloudy no I_2
Dextrose 10 % FeI_2	I_2-crystals	I_2-crystals	broken	solid I_2
Honey 250 cc./L.	scum-no I_2	scum-no I_2	scum no I_2	no I_2
Honey 500 cc./L.	scum-no I_2	scum-no I_2	scum no I_2	no I_2
Honey 50; sucrose 800	good color no I_2	perfect	perfect	trace I_2
Honey 425; sucrose 425	scum-no I_2	scum-no I_2	broken	yellow no I_2
Glycerin 80 %	I_2	I_2	perfect	I_2
Hydroquinone	perfect	perfect	perfect	perfect

Table 78.

Appearance of Samples Stored in the Presence of Air.

6 Months Exposure.

Sample	Dark	Diffused	Sun	Refrig.
U.S.P. control	----	------	---	----
U.S.P. Reagent iron	brown	------	---	----
U.S.P. less H_3PO_2	----	------	---	----

Table 78 - cont.

Appearance of Samples Stored in the Presence of Air.

6 Months Exposure.

Sample	Dark	Diffused	Sun	Refrig.
U.S.P. less H_3PO_2 (Reag. iron)	trace I_2	I_2	---	----
U.S.P. 10 %	---	----	---	----
U.S.P. 0.1975 NaOH	---	----	---	----
U.S.P. 0.3949 NaOH	golden trace I_2	yellow I_2	---	----
U.S.P. 0.6908 NaOH	---	golden I_2	---	----
U.S.P. $Na_2S_2O_3$	I_2	I_2	---	----
Dextrose 10 % FeI_2	crystals	----	---	----
Honey 250 cc./L.	---	----	---	----
Honey 500 cc./L.	---	----	---	----
Honey 50; sucrose 800	I_2	I_2	---	----
Honey 425; sucrose 425	trace I_2	trace I_2	---	----
Glycerin 80 %	---	----	---	----
Hydroquinone	---	trace I_2	---	----

Dashes in the above tabulation indicate that no change has occurred over that recorded in Table 76.

Table 79.

Appearance of Samples Stored in Completely Filled Bottles.

6 Months Exposure.

Sample	Dark	Diffused	Sun	Refrig.
U.S.P. control	brown	ppt.	---	----
U.S.P. Reagent iron	brown	ppt.	---	----
U.S.P. less H_3PO_2	---	---	---	I_2 scum
U.S.P. less H_3PO_2 (Reag. iron)	---	---	---	I_2 scum
U.S.P. 10 %	no I_2	---	---	I_2
U.S.P. 0.1975 NaOH	---	pale green	---	----
U.S.P. 0.3949 NaOH	---	clear	---	----
U.S.P. 0.6908 NaOH	---	---	---	----
U.S.P. $Na_2S_2O_3$	---	---	---	----
Dextrose 10 % FeI_2	---	---	---	----
Honey 250 cc./L.	---	---	---	----
Honey 500 cc./L.	---	---	---	----
Honey 50; sucrose 800	---	---	---	trace I_2
Honey 425; sucrose 425	---	---	---	----
Glycerin 80 %	---	---	---	----
Hydroquinone	---	---	---	----

Dashes in the above tabulation indicate that no further change has occurred over that noted in Table 77.

As indicated by the results tabulated in Tables 76 to 79 inclusive, every sample stored in the presence of sunlight in the presence of air turned black in color with the exception of those containing dextrose and a sucrose-hydroquinone combination. This tends to verify the conclusion previously reached (p 205) that hypophosphorous acid does not, as many investigators have supposed, cause the darkening in Syrup of Ferrous Iodide, although it is probable that it hastens the appearance of discoloration. Moreover, hydroquinone apparently prevents this coloration.

The presence of iodine in practically all of the samples stored in the refrigerator is added evidence that the results previously found as to increase in rate of iodine formation in the cold are accurate, since in this case even the presence of hydroquinone did not prevent the appearance of iodine.

Under ordinary conditions, the U.S.P. samples had begun to darken and a syrup made without a preservative other than sucrose contained iodine, although its appearance is slower if the preparation is made with Reagent iron. This is in accord with the relative rates of decomposition

of the corresponding solutions of ferrous iodide alone.

Honey, used alone, is shown to be very unsatisfactory as a preservative, but solutions of honey and sucrose for this purpose are much more satisfactory since the honey destroys the free iodine and the sucrose lends viscosity to the preparation.

Sodium thiosulfate is not satisfactory as a preservative because of the precipitation of free sulfur; hydroquinone, although satisfactory from a chemical point of view, is contra-indicated on therapeutic grounds; the addition of alkali is not desirable because of the green coloration produced; and glycerin although very good in sunlight is valueless under other conditions.

Results indicated as would be expected, that decomposition is much slower in the absence of air, almost any type of solution being preserved to some extent in well filled bottles. Unfortunately, the pharmacist cannot conveniently dispense or use only completely filled bottles and the U.S.P. sample shows the appearance of dark coloration even under these conditions.

From a study of these results, the following general conclusions were reached:

1. The presence of hypophosphorous acid is not

necessary for the development of the black coloration appearing in Syrup of Ferrous Iodide upon long standing.

2. The black coloration appears much more readily in the presence of sunlight and air than under any other conditions.

3. Since dextrose samples do not show black coloration, the cause of this coloration must lie either in the small quantities of unhydrolyzed sucrose molecules or in the levulose formed.

4. It is probable that the presence of hypophosphorous acid acts catalytically in the formation of black coloration, and that the action is not specific, but rather one of hydrogen ion concentration, since samples containing alkali darken much more slowly than those containing neither acid nor base.

5. The crystalline scum noted by Arny, in samples containing hypophosphorous acid was also noted in this investigation, but this scum was not confined to samples containing acid alone. Furthermore, the scum is readily put back into solution by thorough shaking and may be ferric hydroxide.

6. The storage of solutions of ferrous iodide at low temperature is of negative value, the most suitable conditions being approximately room temperature in diffused light.

7. None of the methods of preservation studied is entirely satisfactory under all conditions.

7. The Stabilization of Syrup of Ferrous Iodide.

Since none of the preservatives investigated in the course of this work proved entirely satisfactory under all conditions, it was concluded that the most practical method of preservation would be the use of hypophosphorous acid to prevent the liberation of free iodine and the addition of dextrose to give the properties of a syrup.

It was shown (p 205), that ferrous iodide solutions containing dextrose and hypophosphorous acid do not deteriorate either by liberation of iodine or by permanent darkening. In order to obtain further information regarding the use of dextrose as a substitute for sucrose in Syrup of Ferrous Iodide, samples were prepared as follows: (a) a U.S.P. sample of Syrup of Ferrous Iodide; (b) a sample of solution of ferrous iodide containing 700 Gm./L. of C.P. dextrose, and the U.S.P. quantity of hypophosphorous acid; (c) a sample similar to (b) using a commercial grade of dextrose donated by Penick and Ford of Cedar Rapids, Iowa; and (d) a sample of solution of ferrous iodide containing 400 Gm./L. of U.S.P. Syrupy Glucose and the prescribed quantity of hypophosphorous acid. All samples were of good color, ranging from colorless in the case of C.P.

dextrose to pale yellow in the case of U.S.P. Glucose. Although lacking in sweetness, the syrups were very palatable. Portions of these four samples were stored in darkness at room temperature, in diffused light at room temperature, in sunlight, in the refrigerator at about 6° C., and in the oven at 50° C., in completely filled tightly-stoppered bottles and in bottles containing excess air. In one month, the U.S.P. samples stored in the oven had darkened, and in two months those stored in sunlight had deteriorated in the same way. No change was observed at the end of four months in any of the samples prepared with dextrose. It was concluded that the use of a combination of dextrose and hypophosphorous acid represents the ideal method of preservation for Syrup of Ferrous Iodide.

V. DISCUSSION OF RESULTS.

The Manufacture of Solutions of Ferrous Iodide. It has been assumed by most investigators that the reaction of direct union between iron and iodine is extremely simple, varying only in the speed at which it passes to completion. The results of this investigation, however, seem to indicate that a greater degree of complexity results than would be expected. It has been shown that solutions of ferrous iodide contain a molar excess of iron over iodine, vary in hydrogen ion concentration,

leave different residues on filtration of the reaction mixture, suffer differing degrees of oxidation and precipitate differently under the same conditions. A further study of the details involved in this reaction was beyond the scope of this investigation, nevertheless, a knowledge of these variations from the accepted course of the reaction represents an addition to our understanding of the preparation.

The Hydrolysis of Ferrous Iodide. As was expected, due to the character of the compound, ferrous iodide hydrolyzes in aqueous solution, the degree of hydrolysis being approximately 0.3 %. Lower pH values of solutions of ferrous iodide containing various sugars was explained on the basis of hydrate formation, although the possibility exists that the degree of hydrolysis was increased due to causes not in evidence. Conditions of primary and secondary equilibrium were found to exist, thus accounting in a measure for the variations in pH of aqueous solutions of ferrous iodide.

The Decomposition of Ferrous Iodide. It was shown that none of the stoichiometric equations previously suggested represent the decomposition of aqueous solutions of ferrous iodide. The decomposition, however, is easily explained by applying dissociation and hydrolysis data.

In short, ferrous iodide ionizes and is slightly hydrolyzed, differences in loss of ferrous iron and appearance of iodine, being due to the difference in ease of oxidation of the two ions. Measurements of the rate of decomposition of aqueous solutions of ferrous iodide indicated that the reaction was of the first order, the specific reaction rate being nearly independent of the concentration or of the surface of liquid exposed. Increase of viscosity up to a certain point was shown to decrease the rate of oxidation of iodide ion, but oxidation was shown to proceed more rapidly at 50° C. and at 6° C. than at 30° C. Solutions prepared with Reagent iron do not decompose so rapidly as do those prepared from card teeth, the difference in rate being due to the presence of dissolved impurities in the solution prepared from card teeth. The appearance of dark coloration in Syrup of Ferrous Iodide was shown to be due either to unhydrolyzed sucrose molecules or to levulose, and not due essentially to hypophosphorous acid.

The Evaluation of Preservatives. Having established the effect of several factors which influence the rate of decomposition of solutions of ferrous iodide, it was possible to measure the efficiency of preservatives in a quantitative fashion. Numerous attempts have been made by other investigators to evaluate these preservatives, but failure to take all factors into account has rendered

their results for the most part invalid, e.g., measurement of preservatives in the presence of limited quantities of air obviously invalidates any comparison of their properties. For the purpose of this investigation, uniform conditions of darkness and temperature were established, excess air was provided and preservatives were used in equivalent molar proportions, thus allowing direct comparisons to be made. Under these conditions, it was found that sucrose, dextrose, honey, lactose and glycerin cause a greater reduction in the rate of iodine formation than would be expected on the basis of the viscosity they impart to the solution. This has been accounted for in the case of sucrose, dextrose, honey and lactose by experiments showing that these carbohydrates react directly with iodine, but glycerin was shown not to react in this fashion. Citric and tartaric acids, on the other hand, while lowering the rate of decomposition, do not result in as great a reduction of this rate as would be expected from viscosity measurements, a result which may be explained on the basis of the known fact that increase in hydrogen ion concentration increases the rate of oxidation of iodide ion.

Further experiments under practical conditions tended to verify all data previously found but did not indicate that any preservative was entirely satisfactory under all conditions and for all purposes.

The reaction between carbohydrate and iodine may be one of substitution in the carbohydrate chain or of oxidation of the aldehyde group in the carbohydrate molecule. Since, however, the total iodide is precipitated immediately by the addition of silver nitrate it appears probable that the reaction is essentially one of aldehyde oxidation with consequent iodine reduction. Although the oxidizing action of iodine in alkaline solution is much more powerful than in neutral or acid solution, numerous cases in which iodine acts as an oxidizing agent in weakly acidulated solutions are known (302). In this connection, the action of honey is of interest, experimental work showing it to reduce iodine at a greater rate than either sucrose or dextrose.

The preservative action of glycerin in the presence of sunlight may, in all probability, be accounted for upon the basis of aldehyde formation with subsequent oxidation. Bierri, Henri and Rane (299) have shown that glycerin acquires reducing properties after exposure to ultra violet rays.

The Stabilization of Syrup of Ferrous Iodide. The experimental data gathered during the course of the investigation rendered the stabilization of the preparation a relatively simple matter. Obviously, since none of the

slower acting preservatives or their combinations were capable of reducing free iodine with sufficient rapidity under all conditions, recourse must of necessity be had to either sodium thiosulfate or hypophosphorous acid. Since the former causes a precipitate of free sulfur to appear in the preparation, it is logical to use the latter and it has been shown that dextrose is the only sugar which will give a stable preparation as regards the appearance of permanent dark coloration either with or without the presence of the acid.

Although C.P., commercial or Syrupy Glucose may be employed as the form of dextrose, the first named gives a clear colorless preparation while the latter is distinctly yellow in color. The use of about 700 Gm./L. of the sugar furnishes a preparation which is sufficiently viscous to have a slow rate of decomposition and yet sufficiently sweet to be palatable. Directions for the manufacture of this preparation in stable form follow:

Iron, in the form of fine, bright wire----	20 Gm.
Iodine----------	60 Gm.
Hypophosphorous Acid----------	5 cc.
Dextrose----------	700 Gm.
Distilled Water, a sufficient quantity,	
To make	1000 cc.

Place the iron in a flask having a capacity of about 500 cc., add the iodine and 200 cc. of distilled water, and shake the mixture occasionally, checking the reaction if necessary by placing the flask in cold

water. When the liquid has acquired a green color and has lost the odor of iodine, heat it to boiling, and filter into the dextrose contained in a beaker. Rinse the flask containing the iron with 240 cc. of hot distilled water, in divided portions, passing the rinsings successively through the filter. Add sufficient distilled water to make about 950 cc., dissolve the dextrose with the aid of a water bath, allow to cool, add the hypophosphorous acid and enough distilled water to make 1000 cc., and strain if necessary.

The wholesale cost of U.S.P. X Syrup of Ferrous Iodide in January, 1934, was $ 1.30 per pint, of which sucrose amounts to about $ 0.05. Thus $ 1.25 remain as the cost of manufacture, other ingredients, profits etc. Since sufficient C.P. dextrose to make 1 pint of the modified preparation costs about $ 0.42 and assuming other costs to be equal in both cases, the price per pint of the stabilized preparation should be about $ 1.67 per pint. On the other hand, if commercial dextrose were used, little variation in price would result from that of the present U.S.P. Syrup of Ferrous Iodide since commercial dextrose is quoted at about $ 0.04 per lb. as compared to sucrose at about $ 0.05 per lb. Obviously, it is advantageous from a financial standpoint to use dextrose, regardless of the quality of the sugar used.

VI. CONCLUSIONS.

1. The process of manufacture of Syrup of Ferrous Iodide is more complex than has been supposed.

2. The use of Reagent iron rather than card teeth furnishes a preparation less liable to deterioration.

3. The quality of the iodine used in the manufacture of Syrup of Ferrous Iodide is of no consequence as to the pH of the resulting preparation, provided that it be at least of U.S.P. grade.

4. The hydrogen ion concentrations of aqueous solutions of ferrous iodide may vary between pH 3.1 and pH 4.4 if they are prepared by direct union in aqueous solution.

5. The degree of hydrolysis of solutions of ferrous iodide corresponding in strength to that of the U.S.P. Syrup of Ferrous Iodide is about 0.3 %.

6. Ferrous iodide preparations do not decompose stoichiometrically by oxidation, but rather by the oxidation of the products of ionization and hydrolysis.

7. Increases in viscosity, or of some factor proportional to viscosity, up to a certain point tend to

slow the rate of oxidation of iodide ion.

8. Limited availability of oxygen results in greatly decreased rates of oxidation.

9. Oxidation of iodide ion proceeds at a greater rate at 50° C. and at 6° C. than at 30° C.

10. The dark coloration other than that due to iodine which appears in Syrup of Ferrous Iodide on long standing has been ascribed by some authors to the presence of hypophosphorous acid. While this acid hastens the hydrolysis of sucrose and may thus hasten the appearance of the coloration, the acid cannot be regarded as the cause of the coloration since Syrup of Ferrous Iodide which contains no hypophosphorous acid whatever, darkens on standing.

11. Under conditions of darkness, excess air and a temperature of 30° C., dextrose, sucrose, lactose and honey act as preservatives both by slowing the oxidation of iodide ion and by reducing free iodine to hydriodic acid.

12. Under conditions of darkness, excess air and a temperature of 30° C., citric and tartaric acids increase the rate of oxidation of iodide ion over that to be

expected from the viscosity they impart to the solution, but result in a net decrease in the reaction rate. In addition, citric acid shows some action on iodine and is a better preservative than is tartaric acid.

13. Alcohol is entirely without value as a preservative for ferrous iodide preparations.

14. Under practical conditions, sucrose, honey, dextrose, glycerin, addition of alkali, increases in concentration, sodium thiosulfate, or combinations of these are of no value as preservatives.

15. The most practical means for the preservation of Syrup of Ferrous Iodide is the use of hypophosphorous acid to prevent the liberation of free iodine and the addition of dextrose rather than sucrose to give the properties of a syrup to the resulting preparation.

16. The most suitable conditions for the storage of U.S.P. Syrup of Ferrous Iodide consist in the use of low temperatures and completely filled, tightly-stoppered bottles.

17. The most suitable conditions for the storage of a preparation of ferrous iodide containing dextrose and hypophosphorous acid consist in the use of completely filled, tightly-stoppered bottles placed in darkness or

diffused light at room temperature.

VII. SUMMARY.

1. The history of Syrup of Ferrous Iodide has been reviewed from the time of its introduction into medicine by Dr. Pierquin in 1824, with special emphasis on the suggested means of preservation. The original formulae are listed and a short resume' of the pharmacopoeial changes undergone by the preparation is given. Various theoretical considerations which must be considered in an investigation of Syrup of Ferrous Iodide are discussed under the titles: (a) Iron Compounds; (b) Hypophosphorous Acid and the Hypophosphites; (c) Hydriodic Acid; (d) Carbohydrates; (e) Oxidation-Reduction Potentials; (f) The Action of Light; (g) Auto-oxidation and Anti-oxidants; and (h) Theories of Decomposition.

2. The scope of this investigation was outlined as consisting of: (a) the evaluation of previous work, especially that of controversial nature; (b) a determination of the degree of hydrolysis of ferrous iodide; (c) a determination of the mechanism of decomposition; (d) the evaluation of preservatives; and (e) the stabilization of Syrup of Ferrous Iodide.

3. In order to determine quickly and accurately, the

ferrous iron content of solutions containing iodide or iodine, a permanganate method was developed. This method consisted of precipitating the iodide or iodine with excess silver nitrate and titrating the ferrous iron with potassium permanganate solution in the presence of hydrogen ions.

4. Solutions of ferrous iodide were prepared by direct union of the elements in aqueous solution, by double decomposition and by solution of the solid salt in water and the pH values noted. Reagent, C.P. and U.S.P. iodine were used as were also Reagent iron and card teeth, it being found that large quantities of solutions prepared by direct union from card teeth tended to have a pH of 3.2 while those prepared from Reagent iron were about pH 4.1. The quality of the iodine used was apparently without effect upon the acidity of the resulting solution and the temperature was likewise without effect. Experiments were performed using card teeth obtained from different sources, but no difference could be found in the resulting solutions. Analyses of the card teeth used showed them to contain carbon and sulfur but the addition of finely divided carbon or ferrous sulfide failed to alter the pH of the resulting solutions significantly. It was shown that a greater amount of oxidation occurred in samples prepared from Reagent iron than in samples prepared from card teeth; in this case, the addition of carbon to reaction mixtures of

Reagent iron and iodine resulted in lowering the degree of oxidation. No evidence of the formation of either gaseous hydrocarbons or carbon dioxide could be obtained during the progress of the reaction.

Solutions in which the iron and iodine were accurately weighed and the residual iron determined, indicated that more iron was consumed during the progress of the reaction than could be accounted for on the basis of the equation

$$Fe + I_2 \rightleftharpoons FeI_2$$

and this excess consumption was found to be greater in the case of Reagent iron than when card teeth were used.

5. A series of experiments was performed under uniform conditions of surface exposure, stirring and temperature from which it was concluded that the time of reaction for the direct union of iron and iodine is not as variable as has been supposed. Carbon did not affect this reaction time.

6. Upon determining the pH values of solutions of ferrous iodide at the time of preparation and again after 12 to 24 hours, it was found that regardless of the original pH value, the solutions increase in acidity with time, coming to a condition of equilibrium at about pH 3.2. Precipitation accompanies this initial increase in acidity,

but after equilibrium is attained, further precipitation may occur without consequent increase in acidity. Solutions maintain a pH of 3.2 over a period of one year or longer. Solutions of ferrous sulfate of comparable concentration show the same phenomenon.

7. The theoretical basis for the hydrolysis of salts containing a multivalent ion was developed upon the grounds used by Denham (282) and applied to solutions of ferrous iodide. In order to determine the degree of hydrolysis of the salt a series of dilutions were made and the pH noted at various concentrations. From these data, the hydrolysis constant was calculated and from these values it was in turn deduced that two equilibria exist, the first at pH $\backsim$ 4.1 and the other at pH 3.2. Hydrolysis in both cases was found to consist predominantly of the reaction

$$FeI_2 + H_2O \rightleftharpoons Fe(OH)I + HI$$

although it appears probable that the secondary equilibrium, i.e., pH 3.2, is complicated by the formation of a heterogeneous system. The degree of hydrolysis at pH 3.2 was found to be about 0.3 %.

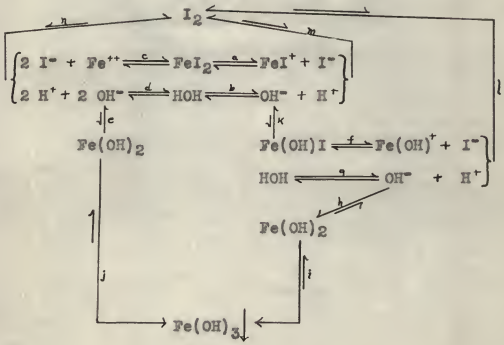
The pH values of solutions of ferrous iodide containing various saccharine substances were also determined, it being found that these values were, in general, lower than

would be expected. By assuming, however, that hydrate formation occurs in the case of the sugar, the apparent concentration of ferrous iodide is increased sufficiently to account for the increased acidity. Calculations using the previously determined hydrolysis constant serve to check the observed pH satisfactorily.

8. By the use of solubility product data it was shown that much less oxidation is necessary for precipitation to occur in the case of Reagent iron samples than in those prepared from card teeth; this is true both for the reaction mixture and for the finished solution of ferrous iodide. Moreover, the solubility of air in water, while providing sufficient oxygen to account for the precipitation of Reagent iron samples, is not sufficiently great to cause immediate precipitation in those prepared from card teeth at a pH of 3.2. This explanation is in accord with the experimental facts. In addition, it was shown that at the hydroxyl ion concentrations of the reaction mixture and of the finished solution, ferrous hydroxide cannot precipitate, nor can ferric hydroxide precipitate in the official Syrup of Ferrous Iodide.

9. The various reactions previously advanced to account for the decomposition of ferrous iodide preparations were shown, without exception, to require on a stoichio-

metric basis the loss of two mols of ferrous iron for each mol of free iodine formed. Samples of ferrous iodide solutions were allowed to decompose under conditions of excess air and of limited oxygen availability at constant temperature and the loss of ferrous iron compared with the quantity of iodine formed. Results showed that no definite quantitative ratio existed between the loss of ferrous iron and the appearance of iodine. An analysis of the precipitates appearing in samples was also made with some indications of the formation of insoluble basic ferrous iodide. Thus from hydrolysis and decomposition data the decomposition of aqueous solutions of ferrous iodide was explained by the following mechanism:



It was stated that this mechanism, in accord with experimental results, also explained the conditions of primary and secondary equilibrium. Thus, we suppose reactions a, b, c, d, e and k to be responsible for the former, while reactions f, g and h are slower due to heterogeneity occasioned by partial precipitation of basic ferrous iodide. Continuous precipitation over long periods of time without increases in acidity were explained on the basis of reactions c, d, e and j which occur to a slight extent without affecting the hydrogen ion concentration of the solution to any appreciable extent. Comparison of the loss of ferrous iron with the appearance of iodine is then shown to be in accord with the oxidation-reduction potentials of the two systems. As further evidence of the validity of the mechanism, it was shown that solutions of ferrous iodide decompose to a greater extent in the presence of excess ferrous or iodide ion. This result, due to its accordance with those of Husa and Shattuck (286) on iodide ion oxidation, would indicate that the decomposition of ferrous iodide is essentially one of iodide ion oxidation occurring separately from ferrous ion oxidation.

10. Experiments were performed to determine the rate of oxidation of iodide ion under conditions of darkness,

excess air and a constant temperature of 30° C. Results were treated according to the velocity equations for first and second order reactions and by the constancy of the first order specific reaction rate, it was concluded that the first order velocity equation may be used to represent this decomposition. This conclusion was further substantiated by similar determinations made upon solutions of different concentrations. Similar calculations showed that the rate of decomposition was not affected, within certain limits, by the surface of the liquid exposed and that the reaction therefore could not be considered to be of the zero order except under conditions of very slow oxygen infiltration or extremely small surface exposure.

Experimentation showed that the rate of decomposition was about twice as great for samples prepared from card teeth as for samples from Reagent iron, the increase in rate being ascribed to the formation of galvanic elements due to impurities present in the card teeth.

The effect of viscosity in solutions of ferrous iodide made viscous by the addition of tragacanth upon the rate of oxidation of iodide ion was measured, it being found that at 30° C. the rate of oxidation was a hyperbolic function of the viscosity or of some factor proportional

to the viscosity, the curve undergoing the greatest change between relative viscosities of 1.0 and 6.0 compared to water at the same temperature. At 50° C., results were not entirely valid, it being found that due to increasing hydration of the tragacanth at this temperature, viscosity was a variable rather than a constant factor, but by the use of data obtained during the early stages of the decomposition, it was shown that a hyperbola would express the variation. At 6° C. the variation of specific reaction rate with viscosity, or of some factor proportional to viscosity, no longer was a hyperbolic function, but assumed instead, the proportions of a straight line.

The effect of temperature alone upon solutions of ferrous iodide was measured and results indicated that these solutions deteriorated more rapidly at 50° C. and at 6° C. than at 30° C.

The absence of oxygen was shown to slow the rate of oxidation of iodide ion tremendously, some evidence apparently existing for the supposition that iodide ion decomposes to a greater extent than can be accounted for upon the basis of the dissolved oxygen present.

The effect of various spectrum bands upon the rate of decomposition was tested by the use of selective light filters and quartz flasks for the ultra violet region of

the spectrum. It was found that no marked acceleration resulted in any case, the uniformly greater reaction rates being attributed to the effects of the entire spectrum and the increased temperature.

11. In an investigation of the permanent dark coloration other than that due to iodine, appearing in Syrup of Ferrous Iodide, various substances present in the syrup were tested as to their action on sucrose solutions alone. It was found that hypophosphorous acid, phosphoric acid and ferrous iron tended to produce a dark coloration in simple syrup, but that iodine was slowly converted to a colorless compound without final change in the color of the syrup. Samples of Syrup of Ferrous Iodide, and samples of Syrup of Hydriodic Acid, which also contains hypophosphorous acid were found to darken and contain a similar dark colored precipitate. On the other hand, samples of Syrup of Ferrous Iodide prepared without hypophosphorous acid were also found to turn dark in color. It was concluded that the black coloration in Syrup of Ferrous Iodide is due either to a compound of the iron and sugar or to decomposition products of the sugar alone. Further experiments showed that samples prepared with dextrose alone, do not become black and it was concluded that the cause of final darkening in Syrup of Ferrous Iodide is due either to decomposition products of sucrose or levulose

or to a compound between iron and sucrose or levulose.

12. The value of various of the most practical preservatives previously mentioned in the literature was measured, first, by testing their effect under conditions of darkness and excess air at a temperature of 30° C. and secondly, by observing their effect under practical storage conditions. Honey, dextrose, sucrose, lactose, citric acid, tartaric acid, sodium thiosulfate, glycerin, alcohol, hydroquinone and the addition of alkali were investigated. It was found that all of these substances except alcohol acted as preservatives, nevertheless, none are ideal. Honey, sucrose, dextrose, lactose and citric acid were shown to exert some action upon free iodine in darkness in aqueous solution at 30° C. and honey and sucrose were shown to remove free iodine from a syrup under these conditions. Experiments in the oven at 50° C. indicated, moreover, that this reaction was much more rapid and had a higher temperature coefficient than the auto-oxidation. Although citric and tartaric acids lowered the rate of formation of free iodine due to the viscosity they imparted to the solution, the specific reaction rate was greater than in solutions of similar viscosity prepared from an indifferent substance, thus indicating that the increase in hydrogen ion concentration increased the rate of decomposition. Glycerin showed some preservative action in

darkness at 30° C., although it does not react with free iodine under these conditions; upon exposure to sunlight, however, perfect preservation results. Sodium thiosulfate proved objectionable because of the liberation of free sulfur; hydroquinone is objectionable from a therapeutic standpoint; alcohol is valueless; and lactose does not give sufficient viscosity nor sweetness due to its low solubility. The addition of alkali was apparently of some value as a preservative, but the green precipitate produced in the solution was objectionable.

In general, exposure to sunlight was found to hasten the formation of dark coloration other than that due to iodine, except in the case of a sample prepared from dextrose which does not darken under any conditions. Storage in a cool place resulted in greatly retarding the appearance of this coloration. On the other hand, solutions were shown to liberate iodine more rapidly in a cool place than at room temperature.

13. From the results of this investigation, it was found that Syrup of Ferrous Iodide could be stabilized by using dextrose in place of sucrose and using hypophosphorous acid as in the present U.S.P. formula. The replacement of sucrose by dextrose elimimates the permanent dark coloration, while hypophosphorous acid prevents the

formation of free iodine. It was found that 700 Gm./L. of dextrose gives an excellent preparation, either C.P. dextrose or commercial dextrose being satisfactory, the former furnishing a nearly colorless preparation. Experimental evidence to show that preparations made in this way are extremely stable and a formula and method of procedure are appended.

Optimum conditions of storage for Syrup of Ferrous Iodide, U.S.P. X, are given as consisting of storage in a cool place in completely filled, tightly-stoppered bottles; those for the modified preparation are stated to be storage at room temperature in diffused light or in darkness, in completely filled, tightly-stoppered bottles.

VIII. BIBLIOGRAPHY.

(1) Courtois, Ann. chim. phys., [1] 88 (1813), 308.

(2) A. C. Wooton, "Chronicles of Pharmacy", MacMillan and Co., London, 1910, Vol. 1, p. 352.

(3) John C. Krantz, Jr., (ed), "Fighting Disease with Drugs", Williams and Wilkins, Baltimore, 1931, 1 st ed., p. 95.

(4) E. Durand, Am. J. Pharm., 4 (1833), 287.

(5) Caillot, Ann. chim. phys., [2] 22 (1823), 136.

(6) Pierquin, Repert. Pharm., 38 (1831), 451.

(7) Baup and Caillot, Am. J. Pharm., 1 (1830), 201.

(8) E. Durand, Am. J. Pharm., 4 (1833), 287.

(9) A. T. Thompson, London Pharm. Trans.; through Am. J. Pharm., 14 (1843), 56.

(10) C. Frederking, Repert. Pharm., 65 (1839), 370.

(11) Editor, Repert. Pharm., 60 (1837), 157.

(12) DuMenil, Arch. Pharm., 7, p. 56; through J. pharm. chim., [2] 21 (1835), 678.

(13) E. F. Anthon, Repert. Pharm., 58 (1836), 261.

(14) A. Henry, J. pharm. chim., [2] 13 (1827), 403.

(15) William Proctor, Jr., Am. J. Pharm., 10 (1840), 13.

(16) Dupasquier, J. pharm. chim., [2] 27 (1841), 117.

(17) Beral, Am. J. Pharm., 13 (1842), 74.

(18) W. Tozier, Am. J. Pharm., 25 (1853), 58.

(19) B. J. Crew, Am. J. Pharm., 26 (1854), 8.

(20) Samuel Battley, Am. J. Pharm., 19 (1847), 64.

(21) Creuse, Am. J. Pharm., 16 (1840), 214.

(22) H. A. Langenhan and C. J. Bradford, J. Am. Pharm. Assoc., 16 (1927), 336, 433.

(23) A. B. Squire, Ann. Philosophy, (1836), 79; through Am. J. Pharm., 14 (1843), 56.

(24) P. Mialhe, Arch. Pharm., 88 (1844), 75.

(25) C. G. Wittstein, Repert. Pharm., 82 (1843), 194.

(26) Jonas, Arch. Pharm., 109 (1849), 257.

(27) John M. Maisch, Am. J. Pharm., 27 (1855), 218.

(28) W. C. Chapman, Am. J. Pharm., 31 (1859), 559.

(29) E. Fougera, Am. J. Pharm., 32 (1860), 22.

(30) W. H. Pile, Am. J. Pharm., 32 (1860), 299.

(31) H. A. Langenhan and C. J. Bradford, J. Am. Pharm. Assoc., 16 (1927), 561, 656.

(32) Daniel Wright, Am. J. Pharm., 26 (1854), 6.

(33) Vesa, J. pharm. chim., 42 (1862), 338.

(34) E. Fougera, Am. J. Pharm., 36 (1864), 307.

(35) Neues. Jahrb. Pharm., 21 (1864), 159; through Proc. A. Ph. A., 12 (1864), 82.

(36) Thos. H. Holloway, Pharm. J., 9 (1867), 471.

(37) Wm. A. Tilden, Pharm. J., 9 (1867), 260.

(38) I. Hughes, London J. Pharm., (Nov. 1868), 32; through Proc. A. Ph. A., 17 (1869), 158.

(39) E. R. Squibb, Am. J. Pharm., 40 (1868), 99.

(40) F. F. Meyer, Proc. A. Ph. A., 7 (1859), 371.

(41) Jeannel, Bull. soc. pharm. Bordeaux; through J. pharm. chim., [4] 8 (1868), 363.

(42) E. R. Squibb, Proc. A. Ph. A., 17 (1869), 343.

(43) Beardsworth, Year Book of Pharm. and Trans., 7 (1870), 58.

(44) Robert Hunstock, Am. J. Pharm., 47 (1875), 390.

(45) J. P. Remington, Am. J. Pharm., 47 (1873), 386.

(46) G. H. Charles Klie, Am. J. Pharm., 53 (1881), 4.

(47) Tizier, Am. J. Pharm., 27 (1851), 89.

(48) Wayne, "U. S. Dispensatory", J. B. Lippincott, Philadelphia and London, 1875, 13 th ed., p. 1433.

(49) W. H. Pile, Proc. A. Ph. A., 24 (1876), 492.

(50) J. E. Judge, Am. J. Pharm., 49 (1876), 159.

(51) A. Hammer, Pharmacist, (April, 1876), 99; through Proc. A. Ph. A., 24 (1876), 102.

(52) R. Rother, Pharmacist, (July 1876), 192; through Proc. A. Ph. A., 25 (1877), 105.

(53) Carol Pavesi, Giorn. farm. Torino; through Proc. A. Ph. A., 27 (1879), 311.

(54) J. E. Gregory, New Remedies, (1878), 110; through Year Book of Pharm. and Trans., 15 (1878), 329.

(55) Thomas B. Groves, Drug. Circ., 24 (1880), 179.

(56) E. W. Runyon, New Remedies, (March, 1880), 66; through Proc. A. Ph. A., 28 (1880), 77.

(57) P. Carles, Bull. soc. pharm. Bordeaux, 20 (1880), 112.

(58) G. F. Schacht, Year Book of Pharm. and Trans., (1882), 496.

(59) Uggeri Francesco, Boll. Farm., (1883), 155; through Proc. A. Ph. A., 32 (1884), 79.

(60) Izard, Am. J. Pharm., 55 (1883), 402.

(61) Preliminary Draft of N. F., Proc. A. Ph. A., 34 (1886), 267.

(62) A. E. Robinson, Year Book of Pharm. and Trans., (1885), 484.

(63) Sylvio Plevani, Pharm. Zeit., (1885), 9.

(64) Otto G. Miller, Western Druggist, (1886), 331; through Proc. A. Ph. A., 35 (1887), 78.

(65) Val Schmidt, Pharmaceutical Record, (1886), 89; through Proc. A. Ph. A., 35 (1887), 353.

(66) J. Lewis Nebinger, Am. J. Pharm., 58 (1886), 86.

(67) Leo Eliel, Pharmaceutical Record, (1888), 213; through Proc. A. Ph. A., 37 (1889), 408.

(68) Joseph England, Am. J. Pharm., 60 (1888), 547.

(69) Nicot, Bull. Gen. de Therap., (July 30, 1888), 188; through Am. J. Pharm., 60 (1888), 449.

(70) Charles Arthur, Am. J. Pharm., 60 (1888), 609.

(71) Zelinka, Pharm. Post., (1888), 794; through Proc. A. Ph. A., 37 (1889), 408.

(72) John Devine, Proc. A. Ph. A., 37 (1889), 124.

(72) Charles Arthur, Am. Druggist, (1890), 92; through Proc. A. Ph. A., 38 (1890), 333.

(73) J. M. Good, Proc. Mo. Pharm. Assoc., (1891), 67; through Proc. A. Ph. A., 39 (1891), 329.

(74) E. A. Warren, Pharmaceutical Record, 13 (1892), 89; through Proc. A. Ph. A., 40 (1892), 503.

(75) A. L. Beck, Am. J. Pharm., 64 (1892), 18.

(76) Siboni, Proc. A. Ph. A., 40 (1892), 503.

(77) A. P. Micas, Pharm. Era, 6 (1892), 263.

(78) Scheerer, Z. oesterr. apoth-verein, (1892), 312; through Proc. A. Ph. A., 41 (1893), 453.

(79) Hugo T. C. Martin, Proc. A. Ph. A., 40 (1892), 503.

(80) J. Martinson, Pharm. Zeit. f. Russl, (1895), 100; through Am. J. Pharm., 65 (1893), 220.

(81) Hanzlik, Pharm. Zeit., No. 37, (1892).

(82) Am. Druggist, (1893), 343; through Proc. A. Ph. A. 41 (1893), 453.

(83) C. T. Roberts, Am. J. Sci., (1893), 126; through Proc. A. Ph. A., 42 (1894), 1004.

(84) Rousillon, J. pharm. chim., 28 (1893), 243.

(85) D. Walker, Proc. A. Ph. A., 45 (1897), 221.

(86) O. Schobert, Pharm. Zeit., (1893), 298.

(87) Austa Worthrup, Proc. A. Ph. A., 42 (1894), 669.

(88) William Lyon, Pharm. J., [3] 24 (1894), 863.

(89) Alva Bradley, Proc. A. Ph. A., 42 (1894), 690.

(90) C. Levy, J. pharm. Alsace Lorraine, 20 (1893), 251.

(91) Austa Worthrup, Western Druggist, (1895), 238; through Proc. A. Ph. A., 43 (1895), 606.

(92) Joseph Ince, Pharm. J., 61 (1896), 128, 142.

(93) J. W. Goodwyn, Proc. Ga. Pharm. Assoc., (1895); through Proc. A. Ph. A., 43 (1895), 639.

(94) Bourquelot, J. pharm. chim., 30 (1895), 171; through Pharm. Zeit., 36 (1895), 452.

(95) George E. Barksdale, Proc. Va. Pharm. Assoc., (1897), 64; through Proc. A. Ph. A., 46 (1898), 729.

(96) A. R. L. Dohme, Proc. Md. Pharm. Assoc., (1897), 40; through Proc. A. Ph. A., 46 (1898), 728.

(97) Proc. A. Ph. A., 47 (1899), 459.

(98) F. R. Macy, Canadian Journal of Pharmacy, (1897), 77; through Proc. A. Ph. A., 46 (1898), 728.

(99) F. W. Haussmann, Drug. Circ., 43 (1899), 221.

(100) William Lyons, Pharm. J., 65 (1900), 754.

(101) H. P. Madsen, Apoth. Ztg., (July 7, 1900), 460.

(102) H. Lionel Meredith, Proc. Md. Pharm. Assoc., (1900), 754; through Proc. A. Ph. A., 46 (1898), 728.

(103) Debrage, J. pharm. chim., [6] 11 (1900), 6.

(104) E. V. Howell, Proc. N. C. Pharm. Assoc., (1902), 62; through Proc. A. Ph. A., 51 (1903), 664.

(105) Daniel Base, Proc. A. Ph. A., 52 (1904), 573.

(106) A. Schleimer, Merck's Report, (1903), 158.

(107) Paul Caldwell, Drug. Circ., 49 (1905), 220.

(108) Paul Caldwell, Southern Drug Journal, (1903), 186; through Proc. A. Ph. A., 52 (1904), 570.

(109) H. A. B. Dunning, Drug. Circ., 49 (1905), 45.

(110) William C. Toplis, Proc. A. Ph. A., 58 (1910), 1258.

(111) W. C. Alpers, J. A. Ph. A., 3 (1914), 422.

(112) John K. Thum, Proc. A. Ph. A., 58 (1910), 1261.

(113) W. C. Alpers, J. A. Ph. A., 3 (1914), 420.

(114) O. J. Cloughly, Proc. Mo. Pharm. Assoc., (1912), 133; through Year Book A. Ph. A., 1 (1912), 65.

(115) Noblet, Pharm. Zeit., 58 (1913), 729.

(116) Paul Bohrisch, Pharm. Zentralh., 54 (1913), 15.

(117) Charles F. Carter, Am. J. Pharm., 67 (1895), 362.

(118) W. A. Shenstone, Pharm. J. [3] 5 (1875), 781.

(119) Chemist Druggist, 15 (1873), 48.

(120) B. S. Proctor, Year Book of Pharm. and Trans., (1882), 508.

(121) L. Myers Connor, Proc. A. Ph. A., 25 (1877), 411.

(122) Proc. A. Ph. A., 25 (1877), 563.

(123) George M. Beringer, J. A. Ph. A., 3 (1914), 971.

(124) William F. Kaemmerer, Proc. A. Ph. A., 50 (1902), 538.

(125) F. W. Haussmann, Am. J. Pharm., 73 (1901), 17.

(126) F. F. Berg and H. E. Becker, J. A. Ph. A., 18 (1929), 503.

(127) H. V. Arny and Abraham Steinberg, J. A. Ph. A., 20 (1931), 1157.

(128) H. V. Arny and Abraham Steinberg, J. A. Ph. A., 20 (1931), 1019.

(129) H. V. Arny, Benjamin Vener and Leslie C. Jayne, J. A. Ph. A., 18 (1929), 265.

(130) John C. Krantz, Jr., J. A. Ph. A., 12 (1923), 964.

(131) E. Mylius, Pharm. Zentralh., 22 (1881), 137.

(132) R. Fresenius, Z. anal. Chem., 6 (1867), 92.

(133) H. Loescoeur, Ann. chim. phys., [7] 2 (1894), 112.

(134) F. Volkmann, J. Russ. Phys. Chem. Soc., (1894); through Ber., 27 (Ref.), (1894), 618.

(135) Charles D. Hodgman and Norbert A. Lange, "Hand Book of Chemistry and Physics", Chemical Rubber Publishing Co., Cleveland, 1930, 15 th ed., p. 218.

(137) Richard Phillips, Jr., Pharm. J. [1] 4 (1844-45), 19.

(138) Horace G. Deming, "General Chemistry", John Wiley and Sons, New York, 1923, p. 396.

(139) Charles D. Hodgman and Norbert A. Lange, "Hand Book of Chemistry and Physics", Chemical Rubber Publishing Co., Cleveland, 1930, 15 th ed., p. 218, 635.

(140) Serrulas; cited by Gmelin-Kraut, "Handbook of Inorganic Chemistry", Leipzig and Berlin, 1872, 6 th ed., Vol. III, p. 350.

(141) Gay-Lussac and Davy, ibid., p. 351.

(142) A. T. Thompson, Pharm. J., 1 (1842), 44.

(143) J. A. Wanklyn and L. Carius, Ann., 120 (1861), 70.

(144) De Luca, Compt. rend., 55, 615; through J. pharm. chim. [3] 43 (1863), 57 and Ann. chim. phys., [7] 2 (1894), 537.

(145) Erdmann, "Lehrbuch der Anorganischen Chemie"; through J. pharm. chim. [3] 43 (1863), 57.

(146) P. Volkmann, Ber. 27, (Ref.), (1894), 618.

(147) C. Loring Jackson and I. H. Derby, Am. Chem. J., 24 (1900), 15.

(148) Horace G. Deming, "General Chemistry", John Wiley and Sons, New York, 1923, p. 473.

(149) Samuel P. Sadtler, Virgil Coblentz and Jeannot Hostmann, "Pharmaceutical and Medical Chemistry", J. B. Lippincott, Philadelphia and London, 1927, 6 th ed., p. 391.

(150) Hubert Thomas Stanley Britton, J. Chem. Soc., 127 (1925), 2110.

(151) Samuel P. Sadtler, Virgil Coblentz and Jeannot Hostmann, "Pharmaceutical and Medical Chemistry", J. B. Lippincott, Philadelphia and London, 1927, 6 th ed., p.391, 393.

(152) E. Müller, Z. Electrochem. angew. physik.-Chem., 14 (1908), 77; cited by Landolt and Bornstein, "Physikalisch-chemische Tabellen", Julius Springer,

Berlin, 1923, 5 th ed., Vol. I, p. 652.

(153) P. P. Von Weimarn, Chem. Reviews, 2 (1925), 217.

(154) Atherton Seidell, "Solubilities of Inorganic and Organic Compounds", D. Van Nostrand, New York, 1919, 2 nd. ed., Vol. I, p. 342.

(155) Goodwin, Z. physik. Chem., 21 (1896), 1; cited by A. Quartaroli, Gazz. chim. ital., 45 (1915), 139; through C. A. 9 (1915), 2016.

(156) Carl Wagner, Kolloid-Z., 14 (1914), 149; through C. A. 8 (1914), 2644.

(157) A. Quartaroli, Gazz. chim. ital., 45 (1915), 139; through C.A. 9 (1915), 2016.

(158) Alfons Krause and W. Buczkowski, Z. anorg. allgem. Chem., 200 (1931), 144; through C. A. 25 (1931), 5860.

(159) G. Malfitano and L. Michel, Compt. rend., 1 (1863), 94; through Proc. A. Ph. A., 11 (1863), 122.

(160) Robert Wintgen and Martin Biltz, Z. physik. Chem., 107 (1923), 403; through C. A. 18 (1924), 1220.

(161) T. Warynski, Ann. chim. anal., (Feb. 15, 1909), 45; through Pharm. J., 32 (1909), 394.

(162) G. Languepin, Bull. soc. pharm. Bordeaux, 28 (1888), 183.

(163) Poiteven, Compt. rend., 1 (1863), 94; through proc. A. Ph. A., 11 (1863), 122.

(164) Wilhelm Moldenhauer and E. Mischke, Z. Electrochem. angew. physik.- Chem., 32 (1926), 252; through C. A. 20 (1926), 2775.

(165) Jacob Cornog and Albert Hirschberger, Proc. Iowa Acad. Sci., 36 (1929), 264; through C. A. 25 (1931), 1146.

(166) Belloni, Chem. Ztg., 1 (1921), 529.

(167) Ad. Paira, Ber., 47 (1914), 1773.

(168) H. Friede, Apoth. Ztg., 45 (1930), 161.

(169) C. Morton, Pharm. J., 127 (1931), 85.

(170) J. B. Lang-Davos, Apoth. Ztg., 47 (1932), 898.

(171) Spencer U. Pickering, J. Chem. Soc., 103 (1913), 1358.

(172) Jan Roszkowski, Z. anorg. allgem. Chem., 14 (1897), 1; through Bull. soc. chim., [3] 18 (1897), 692.

(173) Samuel P. Sadtler, Virgil Coblentz and Jeannot Hostmann, "Pharmaceutical and Medical Chemistry", J. B. Lippincott, Philadelphia and London, 1927, 6 th ed., p. 391.

(174) Putnam, Proc. A. Ph. A., 24 (1876), 626.

(175) A. Duncan Mitchell, J. Chem. Soc., 117 (1920), 957.

(176) Samuel P. Sadtler, Virgil Coblentz and Jeannot Hostmann, "Pharmaceutical and Medical Chemistry", J. B. Lippincott, Philadelphia and London, 1927, 6 th ed., p. 390.

(177) Boyer and Bauzil, J. pharm. chim., 18 (1918), 321.

(178) R. F. Weinland and Walter Hieber, Ber., 52 (1919), 731.

(179) Charles D. Hodgman and Norbert A. Lange, "Handbook of Chemistry and Physics", Chemical Rubber Publishing Co., Cleveland, 1930, 15 th ed., p. 218.

(180) "United States Dispensatory", J. B. Lippincott, Philadelphia and London, 1916, 3 rd ed., p. 51.

(181) Charles D. Hodgman and Norbert A. Lange, "Handbook of Chemistry and Physics", Chemical Rubber Publishing Co., Cleveland, 1930, 15 th ed., p. 635.

(182) G. Lemoine, Pharm. Zentralh., 18 (1877), 396.

(183) J. Pinnow, Ber., 34 (1901), 2528.

(184) J. Plotnikov, Z. physik. Chem., 58 (1907), 214; through G. B. Kistiakowsky, "Photochemical Processes", Chemical Catalog Co., New York, 1928, p. 201, 202.

(185) J. Plotnikov, Z. physik. Chem., 64 (1908), 215; through C. A., 2 (1908), 2034.

(186) H. Jermain Creighton and A. Stanley Mackenzie, Am. Chem. J., 39 (1908), 474.

(187) Kailan, Monatsch., 34 (1913), 1209; through J. Chem. Soc. Abs., 103 (1913), 1030.

(188) William J. Husa and Paul Stanley Shattuck, J. A. Ph. A., 21 (1932), 114.

(189) William J. Husa and Louis Magid, J. A. Ph. A., 22

(1933), 279.

(190) J. U. Nef, Ann., 357 (1907), 214, 403 and Ann., 403 (1913), 204.

(191) Schuchiro Ochi, Proc. World Eng. Congress, Tokyo, (1929), 31 (1931), 537; through C. A. 25 (1931), 5147.

(192) Walter F. Goebel, J. Biol. Chem., 72 (1927), 801.

(193) Richard Willstätter and Gustav Schudel, Ber., 51 (1918), 780.

(194) C. Romijn, Z. anal. Chem., 36 (1897), 349.

(195) G. W. L. Plette, J. A. Ph. A., 7 (1918), 607.

(196) L. Kahlenberg, D. J. Davis and R. E. Fowler, J. Am. Chem. Soc., 21 (1899), 1.

(197) Frederick H. Getman and Farrington Daniels, "Outlines of Theoretical Chemistry", John Wiley and Sons, New York, 1931, 5 th ed., p. 330.

(198) F. W. Haussmann, Am. J. Pharm., 70 (1898), 585.

(199) J. H. Zisch, Sugar Press, 10, No. 6-16; through C.A. 21 (1927), 189.

(200) H. A. Spoehr, J. Am. Chem. Soc., 46 (1924), 1494.

(201) H. A. Spoehr, ibid., 48 (1926), 236.

(202) A. Ganguli and A. B. Malkani, J. phys. Chem. 35 (1931), 2364; through C. A. 25 (1931), 5613.

(203) Eugene Peligot, Ann. chim. phys., [2] 67 (1838), 172; Thomas Graham, ibid., [3] 65 (1862), 190, 496.

(204) Wilbur L. Scoville, "The Art of Compounding", P. Blakiston Son's and Co., Philadelphia, 1925, 4 th ed., p. 91-94.

(205) J. Graham, J. Chem. Soc., 15 (1862), 253.

(206) Frank Powis, ibid., 107 (1915), 818.

(207) M. R. Mehrota and K. C. Sen, Quart. J. Indian Chem. Soc., 4 (1927), 117; through C. A. 21 (1927), 3515.

(208) K. C. Sen, ibid., 4 (1927), 131; through C. A. 21 (1927), 3515.

(209) S. I. Hakomari, J. Chem. Soc. Japan, 43 (1922), 629; through Quart. J. Pharm. and Pharmacol., 4 (1931), 451.

(210) W. D. Bancroft, J. Phys. Chem., 20 (1916), 85; through Quart. J. Pharm. and Pharmacol., 4 (1931), 451.

(211) Wilhelm Bachmann, Kolloid-Z., 47 (1929), 49; through C. A. 23 (1929), 2089.

(212) L. Michaelis and E. Friedheim, J. Biol. Chem., 91 (1931), 343.

(213) Roscoe Gerke, Chem. Reviews, 1 (1925), 377.

(214) A. A. Noyes, "Qualitative Chemical Analysis", The MacMillan Co., New York, 1920, 8 th ed., p. 181.

(215) Frederick H. Getman and Farrington Daniels, "Outlines of Theoretical Chemistry", John Wiley and Sons, New York, 1931, 5 th ed., p. 538-553.

(216) Emil Bauer, Helv. Chim. Acta, 1 (1918), 186; through C. A. 13 (1919), 282.

(217) C. Winther and Oxholt-Howe, Z. wiss. Phot., 14 (1914), 196; through C. A. 9 (1915), 748.

(218) Wilbur L. Scoville, J. A. Ph. A., 4 (1915), 590.

(219) J. B. Burt, J. A. Ph. A., 17 (1928), 650.

(220) Thesis, "The Action of Light on Solutions of Soluble Ferric Phosphate", University of Wisconsin, (1915); cited by J. B. Burt, J. A. Ph. A., 17 (1928), 650.

(221) J. Liebig, Ann. 113 (1860), 1.

(222) W. Seekamp, Ann. 278 (1894), 373.

(223) Thesis, "Catalytic Reactions of Sunlight", University of Wisconsin, (1915); cited by J. B. Burt, J. A. Ph. A., 17 (1928), 650.

(224) C. Neuberg, Biochem. Z., 27 (1910), 305; cited by J. B. Burt, J. A. Phl A. 17 (1928), 650.

(225) A. Benrath, Chem. Zentr., II, (1912), 1342; cited by J. B. Burt, J. A. Ph. A., 17 (1928), 650.

(226) H. Shipley Fry and Elmer C. Gerwe, Ind. Eng. Chem., 20 (1928), 1393.

(227) Eder, Ber. 82, (1880), 606; cited by Fry and Gerwe, Ind. Eng. Chem., 20 (1928), 1393.

(228) Vries, Chem. Zentr., 56 (1885), 219; cited by Fry and Gerwe, Ind. Eng. Chem., 20 (1928), 1393.

(229) C. Neuberg, Biochem. Z., 44 (1912), 495; cited by

Fry and Gerwe, Ind. Eng. Chem., 20 (1928), 1393.

(230) E. K. Rideal and E. G. Williams, J. Chem. Soc., 127 (1925), 258.

(231) Carl Wagner, Z. physik. Chem., 113 (1924), 261; through C. A. 19 (1925), 767.

(232) N. Sasoki, Z. anorg. allgem. Chem., 122 (1922), 61, 72; through C. A. 16 (1922), 3441.

(233) J. N. Bronsted and K. Pederson, Z. physik. Chem., 103 (1922), 307; through C. A. 17 (1923), 1745.

(234) Berthollet, J. école polytech., 3 (1797), 277; cited by Nicholas A. Milas, Chem. Reviews, 10 (1932), 295.

(235) C. Englis, Ber., 30 (1897), 1669; A. Bach, Compt. rend., 124 (1897), 951; cited by Nicholas A. Milas, Chem. Reviews, 10 (1932), 295.

(236) R. Luther, Z. physik. Chem., 45 (1903), 662; cited by Nicholas A. Milas, Chem. Reviews, 10 (1932), 295.

(237) C. Moreu and C. Dufraisse, Inst. intern. chemire Solvay, p. 524 (Bruxells, 1925); cited by Nicholas A. Milas, Chem. Reviews, 10 (1932), 295.

(238) Nicholas A. Milas, Chem. Reviews, 10 (1932), 295.

(239) H. Wieland and W. Franke, Ann. 464 (1928), 101.

(240) E. Berl and K. Winnacker, Z. physik. Chem., 148 (1930), 261; cited by Nicholas A. Milas, Chem. Reviews, 10 (1932), 295.

(241) W. Manchot, Ann., 460 (1927), 179.

(242) Nicholas A. Milas, Chem. Reviews, 10 (1932), 298.

(243) Oskar Baudisch and Lars A. Welo, J. Biol. Chem., 61 (1924), 261; cited by Nicholas A. Milas , Chem. Reviews,10 (1932), 298.

(244) Nicholas A. Milas , Chem. Reviews, 10 (1932), 306.

(245) D. R. Hale, J. Phys. Chem., 33 (1929), 1633; cited by Nicholas A. Milas, Chem. Reviews, 10 (1932), 308.

(246) A. B. Lamb and L. W. Elder, Jr., J. Am. Chem. Soc., 53 (1931), 137.

(247) F. O. Schmitt, C. H. Johnson and A. R. Olsen, J. Am. Chem. Soc., 51 (1929), 370.

(248) Richard Phillips, Jr., Pharm. J., [1] 4 (1845), 19.

(249) Fruckhinger, Pharm. Centr. No. 53 (1845); cited by Richard Phillips, Pharm. J., [1] 4 (1845), 426.

(250) Julius Schmidt, "A Text-Book of Organic Chemistry", D. Van Nostrand Co., New York, 1926, p. 736.

(251) F. F. Meyer, Am. J. Pharm., 32 (1860), 171.

(252) Max Tschirner, Am. J. Pharm., 47 (1875), 249.

(253) E. Mylius, Pharm. Zentrelh., 22 (1881), 137.

(254) W. H. Wearn, Proc. A.Ph. A., 40 (1892), 268.

(255) Theodore Salzer, Pharm. Ztg., (1892), 224.

(256) A. H. Woltersdorff and H. G. Richtmann, Pharmaceutical Archives, (1900), pages 81-92, 101-109.

(257) F. W. Haussmann, AM. J. Pharm., 70 (1898), 586.

(258) Jungfleah and Grembart, Bull. soc. chim., [3] 1 (1889), 689.

(259) Felix D'Arcet, Ann. chim. phys.,[2] 37 (1828), 220.

(260) F. W. Haussmann, Am. J. Pharm., 73 (1901), 17.

(261) E. Kimmich, J. A. Ph. A., 4 (1915), 178.

(262) A. V. Pamiflov and N. N. Petin, Bull. Instit. Polytech. Ivanovo Voznesesrk, 6 (1922), 221; through C. A. 17 (1923), 1365.

(263) Arthur Owen Bentley, "Textbook of Pharmaceutical Chemistry", Bailliere, Tindall and Cox, London, 1926, p. 310.

(264) Arthur Owen Bentley and Driver, "Textbook of Pharmaceutical Chemistry", Bailliere, Tindall and Cox, London, 1925, p. 130.

(265) Schissele, J. pharm. Alsace Lorraine, 54 (1927), 99.

(266) W. E. Horn, Proc. Pa. Pharm. Assoc., (1903), p. 111; through Proc. A. Ph. A., 52 (1904), 573.

(267) H. A. B. Dunning, Proc. Md. Pharm. Assoc., (1903); through Proc. A. Ph. A., 52 (1904), 573.

(268) Samuel P. Sadtler, Virgil Coblentz and Jeannot Hostmann, "Pharmaceutical and Medical Chemistry", J. B. Lippincott, Philadelphia and London, 1927, 6th ed., p. 391.

(269) Glenn L. Jenkins and Andrew G. DuMez, "Quantitative Pharmaceutical Chemistry", The McGraw-Hill Book Co.

New York and London, 1931, p. 17.

(270) Ibid., p. 46.

(271) Ibid., p. 62.

(272) Ibid., p. 126.

(273) Ibid., p. 118, 124.

(274) Ibid., p. 87.

(275) Ibid., p. 88.

(276) Sinnat, Analyst, 35 (1910), 309.

(277) R. R. Bennett and T. Tusting Cocking, "The Science and Practice of Pharmacy", J. and A. Churchill, London, 1933, Vol. I, p. 258.

(278) George Lunge and Charles Alexander Keane, "Technical Methods of Chemical Analysis", Gurney and Jackson, London, 1911, Vol. II, Part 1, p. 81.

(279) Glenn L. Jenkins and Andrew G. DuMez, "Quantitative Pharmaceutical Chemistry", The McGraw-Hill Book Co., New York and London, 1931, p. 17.

(280) C. Remegius Fresenius and Alfred I. Cohn, "Quantitative Chemical Analysis", John Wiley and Sons, New York, 1903, Vol. I, p. 323.

(281) Henry George Denham, J. Chem. Soc., 93 (1908), 41.

(282) William C. McC. Lewis, "A System of Physical Chemistry", Longmans, Green & Co., New York and London, 1921, Vol. I, p. 248.

(283) George Scatchard, J. Am. Chem. Soc., 43 (1921), 2406.

(284) Charles D. Hodgman and Norbert A. Lange, "Handbook of Chemistry and Physics", Chemical Rubber Publishing Co., Cleveland, 1930, 15 th ed., p. 548.

(285) William J. Husa and Paul Stanly Shattuck, J. A. Ph. A., 21 (1932), 114.

(286) Winther, Z. Physik. Chem., 108 (1924), 236; through C. A. 18 (1924), 1434.

(287) Frederick H. Getman and Farrington Daniels, "Outlines of Theoretical Chemistry", John Wiley and Sons, New York, 1931, 5 th ed., p. 549.

(288) Ibid., p. 321-334.

(289) S. Glasstone, "The Electrochemistry of Solutions", D. Van Nostrand, New York, 1930, p. 441.

(290) Arthur A. Noyes, "Qualitative Chemical Analysis", The MacMillan Co., New York and London, 1920, 8 th ed., p. 181.

(291) Francis Owen Rice, "Reaction Velocity in Homogeneous Systems" in Hugh S. Taylor (ed.) "A Treatise on Physical Chemistry", D. Van Nostrand, New York, 1924, Vol. II, p. 883.

(292) Frederick H. Getman and Farrington Daniels, "Outlines of Theoretical Chemistry", John Wiley and Sons, New York, 1931, 5 th ed., p. 58.

(293) Berthoud and Nicolet, Helv. Chim. Acta, 10 (1927), 475; J. chim. phys., 25 (1928), 163; cited by

N. R. Dhar, "The Action of Light", Blackie & Co., London and Glasgow, 1931, p. 169.

(294) N. R. Dhar, "The Action of Light", Blackie & Co., London and Glasgow, 1931, p. 169, 173.

(295) Henry Winter, Ann. 244 (1887), 320.

(296) Henry Winter, Ibid., 244 (1887), 323.

(297) Alfred C. Chapman, J. Chem. Soc., 59 (1891), 326.

(298) William J. Husa and Louis Magid, J. A. Ph. A., 22 (1933), 279.

(299) Henry Bierri, Victor Henri and Albert Ranc, Compt. rend., 151 (1910), 516.

(300) E. Canals and Baumelow, Schweiz.-Apoth. Zeit., No 2, (Jan. 14, 1933), 15.

(301) Franklin, Pharm. J., 119 (1927), 581.

(302) William J. Husa and W. W. F. Enz, J. A. Ph. A. 19 (1930), 328.

ADDITIONAL BIBLIOGRAPHY.

Stratingh, Repert. Pharm., 15 (1823), 291.

Oberdorffer, J. pharm. chim., [2] 26 (1841), 587.

Hermann Hager, Pharm. Zentrh., 9 (1868), 296.

Augustine Duhamel, Am. J. Pharm., 10 (1839), 280.

E. Mouchon, Am. J. Pharm., 8 (1837), 253.

T. and H. Smith, Am. J. Pharm., 18 (1847), 102.

Percy Wells, Pharm. J., [3] 14 (1884), 82.

E. J. Mowry, Am. J. Pharm., 58 (1886), 289.

A. Bernick, Pharm. Ztg., (1892), 373.

H. Matuson, Am. J. Pharm., 75 (1903), 71.

O. Linde (Cited by reference No. 111)

Scheling (Cited by reference No. 111)

Constatin-Tomasici (Cited by reference No. 111)

E. Pajetta, Officina, 5 (1932), 261; through C. A. 27 (1932) 1712 and Squibb Abstract Bulletin, 6 (1932), 1296.

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